Clinical Trials

Translational Research : Bench to bedside, Clinical Trials

Jill P Smith, MD
Professor of Medicine
Georgetown University

Disclosures

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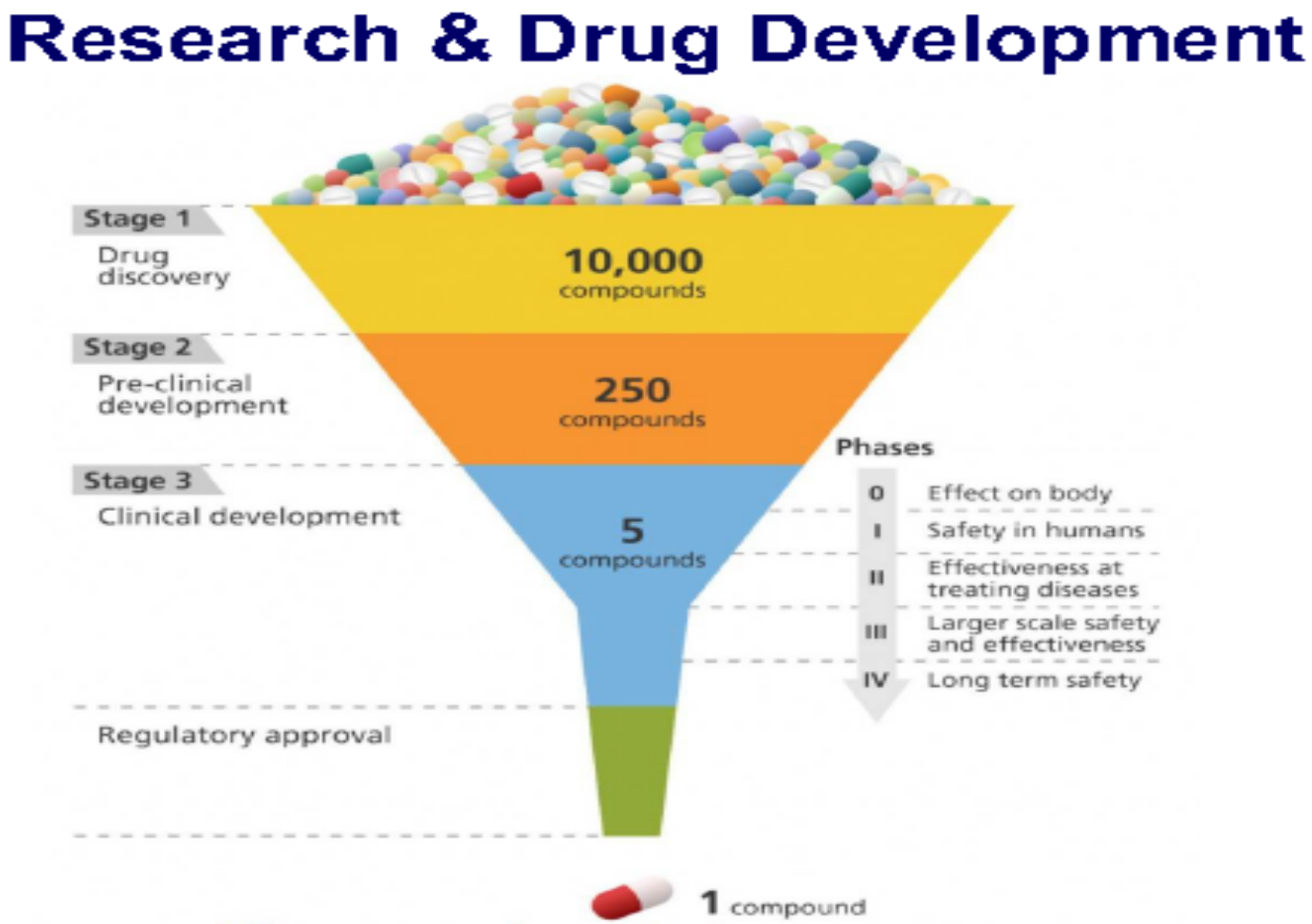
1. Dr. Smith is a co-inventor on 10 patents – some related to pancreatic cancer.
2. Dr. Smith is the Director of Clinical & Translation Research, LLC, a biotech research consulting company
   - Consultant for Immune Therapeutics, Cytocom, and Cato Research, Inc.

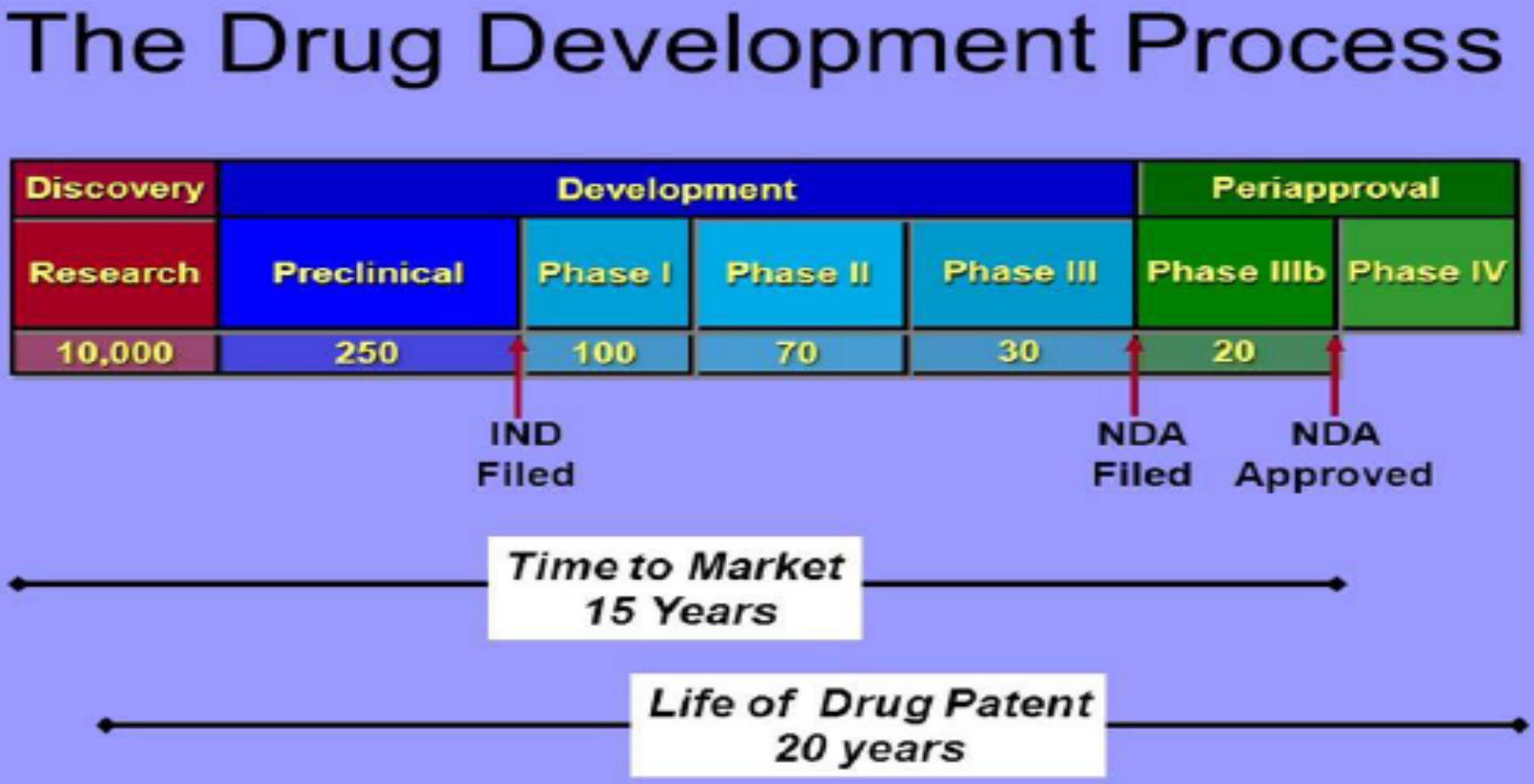
OBJECTIVES

- Understand how an idea is taken from the research lab to patient care.
- Learn the steps in conducting clinical trials
- Comprehend some of the obstacles to overcome in drug development?
- Examples of my translational projects
- Pitfalls and the Prize

Research and drug development



Drug development process



Ideas

You need an Idea

Hypothesis

Passion!!

Drugs and plants

Drugs and wild plants

Drugs Derived from Wild Plants

Plant	Location	Drug	Use
Willow	Worldwide	Aspirin	Fever and pain
Cinchone	Tropics	Quinine	Malaria
Rosy Periwinkle	Madagascar	Vincristine	Leukemia
Rosy Periwinkle	Madagascar	Vinblastine	Hodgkin's disease
Pacific Yew	Pacific Northwest	Taxol	Ovarian cancer
Opium Poppy	Eurasia, Africa	Morphine	Pain
Curare	Amazon	Tubocurarine	Muscle relaxant
Snakeroot	India	Reserpine	Hypertension
Foxglove	Eurasia, Africa	Digoxin	Cardiac arrhythmia

Drug development

Drug Development

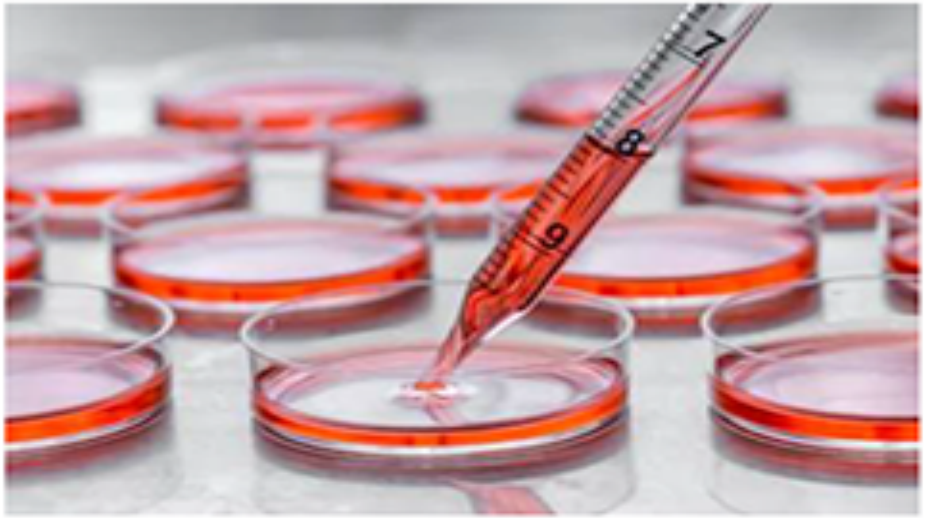
- In the United States, it takes an average of 12 years for an experimental drug to travel from the laboratory to your medicine cabinet.
- Only 5 in 5,000 drugs that enter preclinical testing progress to human testing. One of these 5 drugs that are tested in people is approved. The chance for a new drug to actually make it to market is thus only 1 in 5,000.
- The process of drug approval is controlled in most countries by a governmental regulatory agency. In the U.S., the Food and Drug Administration (FDA) governs this process. The FDA requires the following sequence of events before approving a drug.

Preclinical Testing:
Investigational New Drug Application (IND
Phase I Clinical Trials
Phase II Clinical Trials:
Phase III Clinical Trials:
New Drug Application (NDA):
Phase IV Studies
Although there are other routes that can expedite the process (referred to as fast-tracking

Preclinical studies

Preclinical Studies

Preclinical Testing: research lab conducts certain studies before the future drug is ever given to a human being. Laboratory and animal studies must be done to demonstrate the biological activity of the drug against the targeted disease. The drug must also be evaluated for safety. These tests take on the average 3 1/2 years.



Phase 1

Phase 1

- 15-30 people
- Determines
  - what dose is safe?
  - How the treatment should given?
  - Pharmacokinetics?
  - How the treatment affects the body?
  - Safety & toxicity

How much?

What route of administration?

Pilot Study

Pilot Study

- A small study that helps develop a bigger study
- A first venture into a particular area
- Used to iron out possible difficulties, and help with design of the bigger, more pivotal study.
- Helps provide ‘tentative response rate’ to estimate the sample size needed in a Phase 2 trial to reach significance over control

Natalizumab

PML: Progressive multifocal leukoencephalopathy

Natalizumab: tysabri

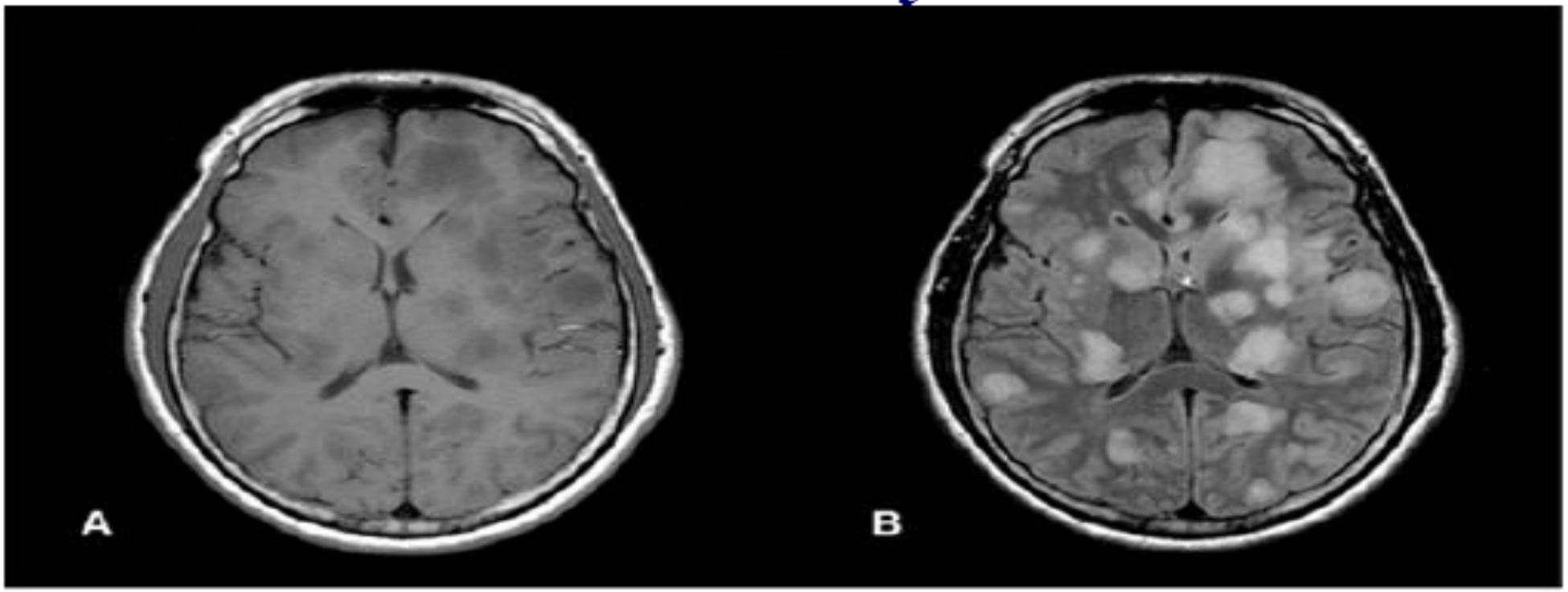


FIGURE 2 - Axial T1-weighted brain magnetic resonance imaging discloses multiple irregular hypointense lesions (A) without mass effect, which are better individualized in the FLAIR sequence (B).

Vioxx

Vioxx

79 of 4,000
Vioxx users suffered
heart problems
or died

Vioxx is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID).

Phase 1

Phase 1: first in human trial

- Study the safety and toxicity of drug in humans
- Determine the Maximum-Tolerated Dose (MTD)
- Study the biological kinetics and metabolism of OGF (Pharmacokinetics)
- Study the route of administration

25g → 70kg

Calculating human dose

Calculating human dose from animal study

Nair AB, Jacob S. Journal of Basic and Clinical Pharmacy. 2016;7(2):27-31.

Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED in mg/kg, either	
					Divide animal dose by	Multiply animal dose by
Human	60	-	1.62	37	-	-
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.08	0.047-0.157	0.016	5	7.4	0.135
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Monkeys (rhesus)	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162
Squirrel monkey	0.60	0.29-0.97	0.09	7	5.3	0.189
Baboon	12	7-23	0.60	20	1.8	0.541
Micro pig	20	10-33	0.74	27	1.4	0.730
Mini pig	40	25-64	1.14	35	1.1	0.946

*Data obtained from FDA draft guidelines.[7] FDA: Food and Drug Administration, HED: Human equivalent dose

The dose by factor method applies an exponent for body surface area (0.67), which account for difference in metabolic rate, to convert doses between animals and humans. Thus, HED is determined by the equation:

$$\text{HED (mg / kg} = \text{Animal NOAEL mg/kg}) \times (\text{Weight}_{\text{animal}}\ [\text{kg}]/\text{Weight}_{\text{human}}\ [\text{kg}])^{(1-0.67)}$$

[no observed adverse effect levels (NOAEL) from preclinical research]

Phase 2

Phase 2: Efficacy

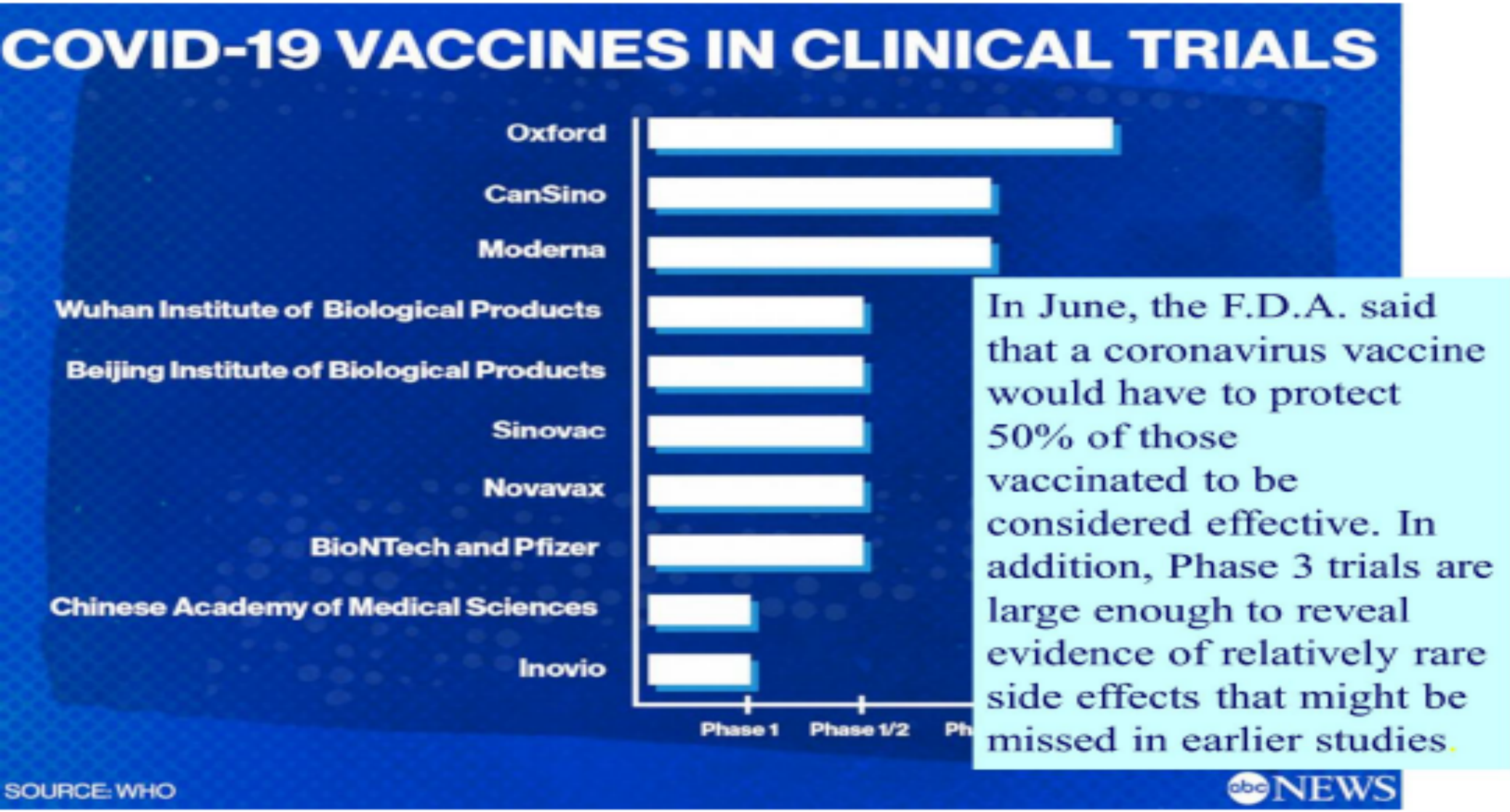
- Less than 100 people
- Must have a primary endpoint
- Usually unbiased (blinded)
- Determines
  - Does it work?
  - Is it more effective than a placebo?
  - Does not compare with other treatments

Randomized clinical trials

Phase 2: Randomized Clinical Trials

- Equal chance to be assigned to one of two or more groups
  - One group gets the most widely accepted treatment (standard treatment) or placebo
  - The other gets the new treatment being tested
- All groups are as similar as possible
- Provides the best way to prove the effectiveness of a new agent or intervention

COVID-19 vaccines



Phase 3

Phase 3

- From 100 to thousands of people
- Equal chance to be assigned to one of two or more groups
- Determines
  - How the new treatment compares with the current standard
  - Or how it compares with placebo
  - Superiority or non-inferiority trials

Phase 4

Phase 4

- From hundreds to thousands of people
- Usually takes place after drug is approved to provide additional information on the drug's risks, benefits and optimal use
- Called 'Post-marketing" or

Or post-approval trials

Patient rights

How Are Patients' Rights Protected?

- Ethical and legal codes that govern medical practice also apply to clinical trials
- Informed consent
- Review boards
  - Scientific review
  - Institutional review boards (IRBs)
  - Data safety and monitoring boards

Genetic testing
Add to consent

IND

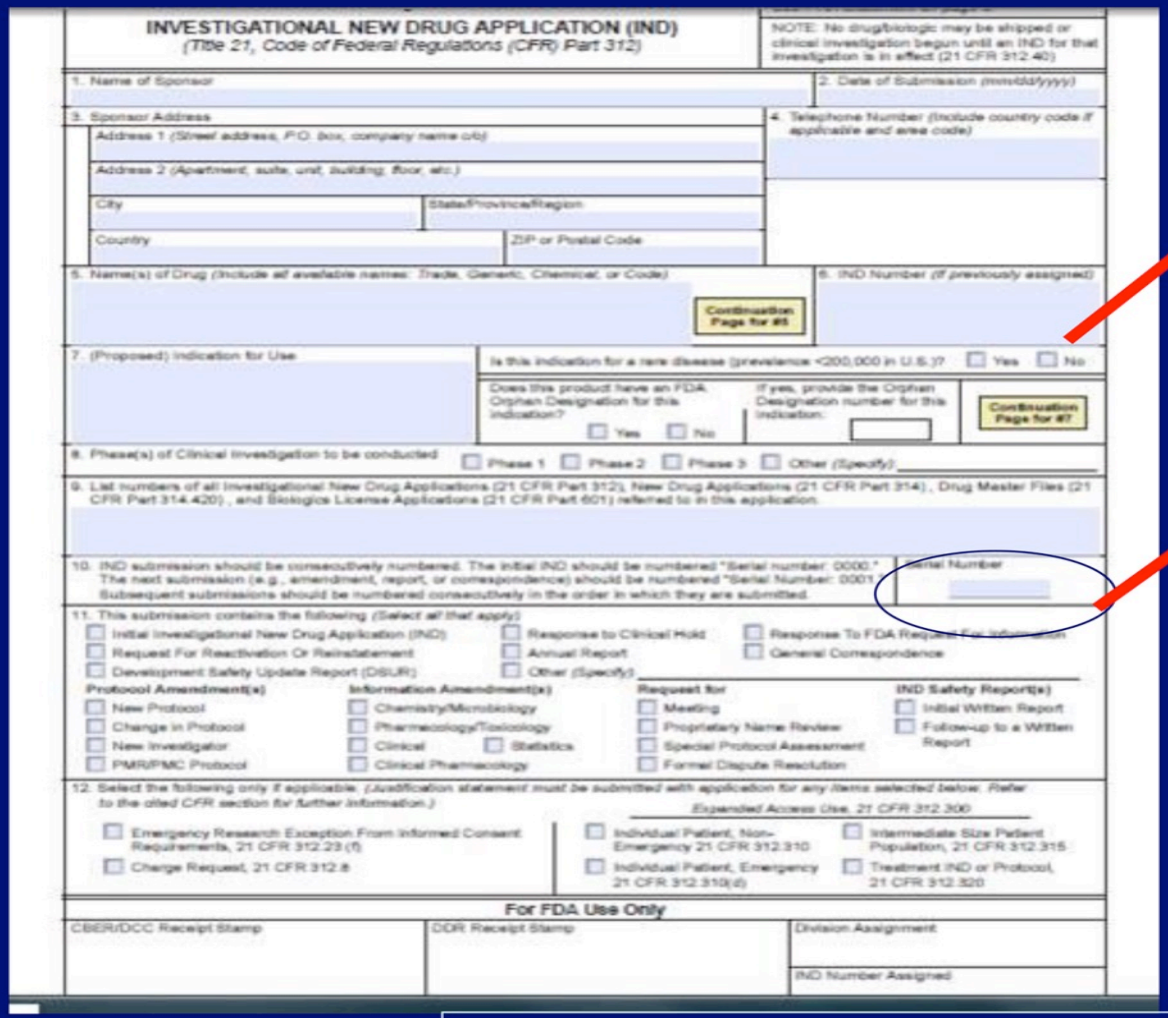
Investigational New Drug (IND) Application

- **Need approval from FDA**
  - **Apply for and IND# (investigational new drug#)**
  - **1571 and 1572**

The IND becomes effective if the FDA does not disapprove it within 30 days.
The IND must include the following information: the results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. The IND must also be reviewed and approved by the Institutional Review Board where the studies will be conducted.

FDA forms

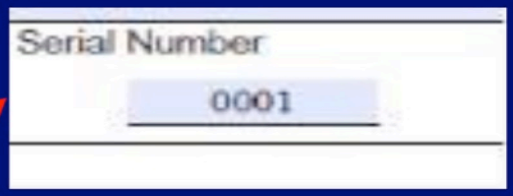
FDA 1571 and 1572 forms, info about sponsor & drug



INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
6. IND Number (If previously assigned)
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted: Phase 1 Phase 2 Phase 3 Other (Specify)
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.
Serial Number
11. This submission contains the following (Select all that apply)
Initial Investigational New Drug Application (IND)
Request For Reactivation Or Reinstatement
Development Safety Update Report (DSUR)
Response to Clinical Hold
Annual Report
Other (Specify)
Response To FDA Request For Information
General Correspondence
Protocol Amendment(s)
New Protocol
Change in Protocol
New Investigator
PMR/PMC Protocol
Information Amendment(s)
Chemistry/Microbiology
Pharmacology/Toxicology
Clinical
Statistics
Clinical Pharmacology
Request for
Meeting
Proprietary Name Review
Special Protocol Assessment
Formal Dispute Resolution
IND Safety Report(s)
Initial Written Report
Follow-up to a Written Report
12. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320
For FDA Use Only
CBER/DCC Receipt Stamp
DDR Receipt Stamp
Division Assignment
IND Number Assigned



What are you Submitting or requesting In this report

Must be submitted with <u>every</u> communication to FDA

Intellectual Property

Intellectual Property

- Submit an invention disclosure and provisional patent before you present the research results publically (including abstracts).
- The patent belongs to whomever you worked for when you made the discovery. If your employer does not want to file a patent have them assign the rights to you.

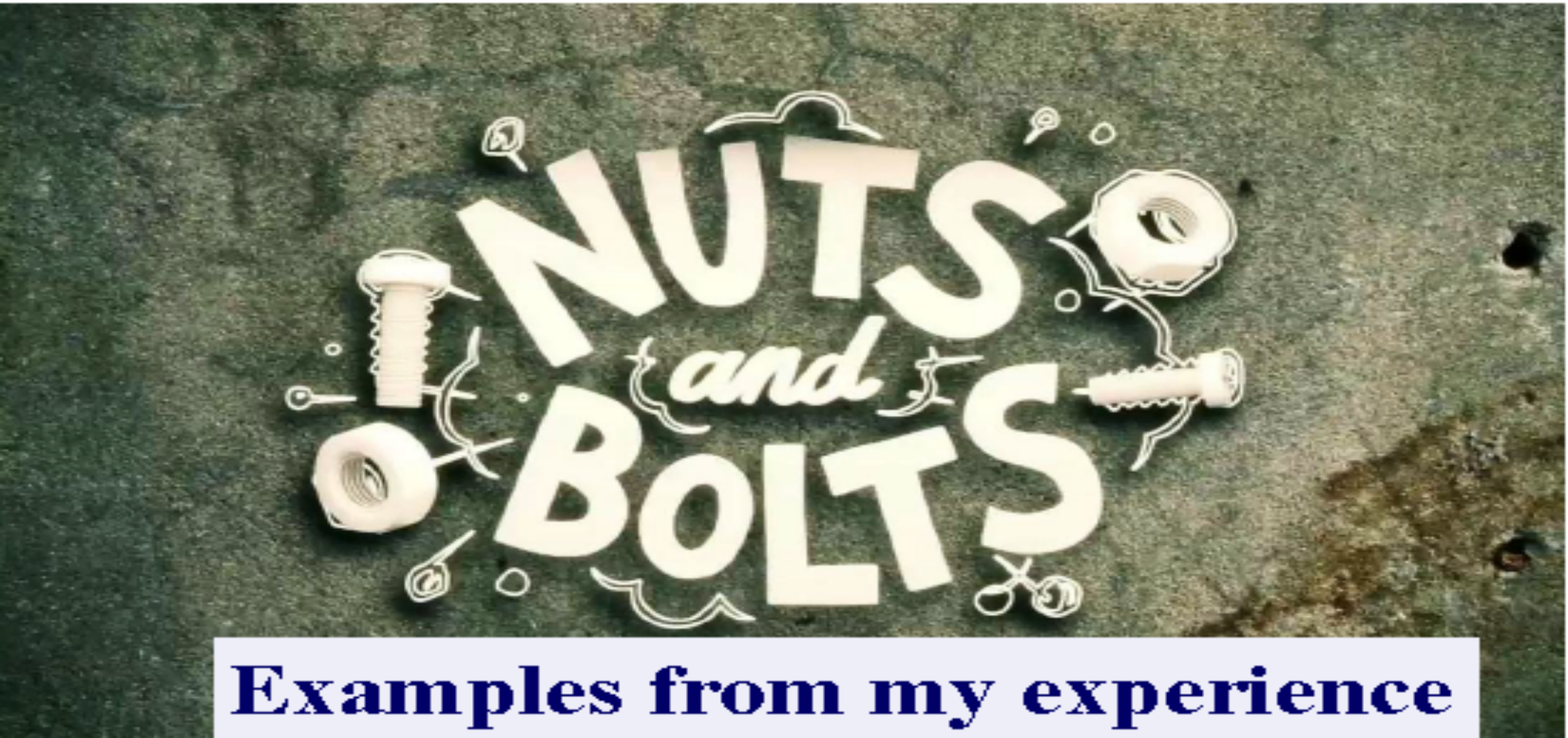
Clinical trials

Other things to do for a Clinical Trial

- Write a protocol- study design with outcomes
- Write a consent form
- Obtain IRB approval
- Find a Sponsor - Get Funding support-$
- Responsibilities of the Principal Investigator (CITI training)
- Research Nurse /Study coordinator
- Registration of clinical trial on www.clinicaltrials.gov

Nuts and bolts

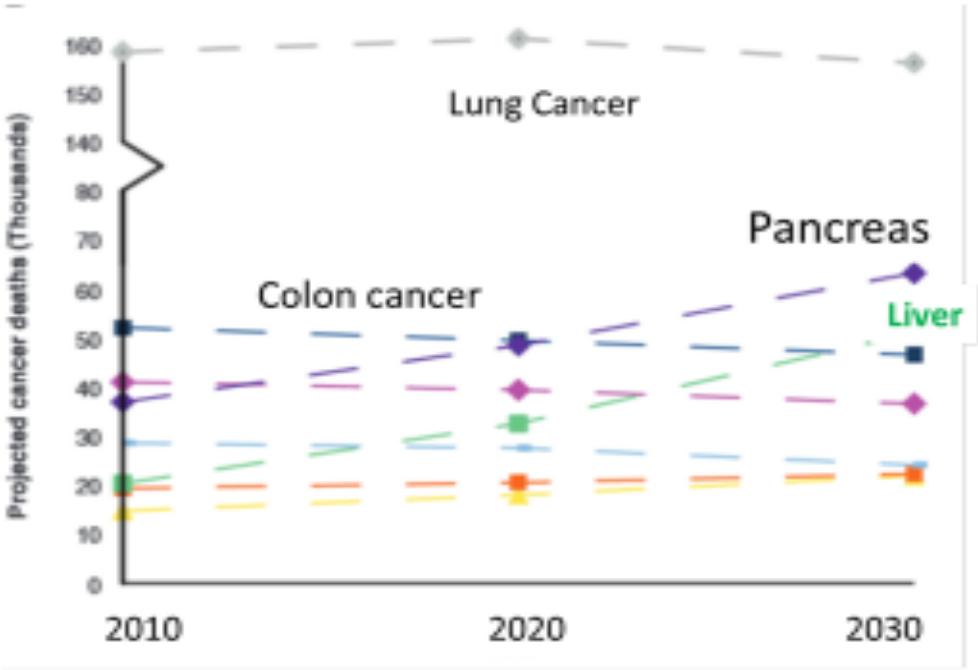
How Do You Do It?



Pancreatic cancer research

My Research in Pancreatic cancer

- 2nd leading cause of cancer-related deaths in the United States; about 58,000/yr
- The median survival with Standard of Care therapy less than 1 year
- Five year survival is approximately 9.3%.
- Most cases are not diagnosed in the early stages- 90% are not resectable.
- 85-90% arise from Precursor PanIN lesions
- 90% have no family history



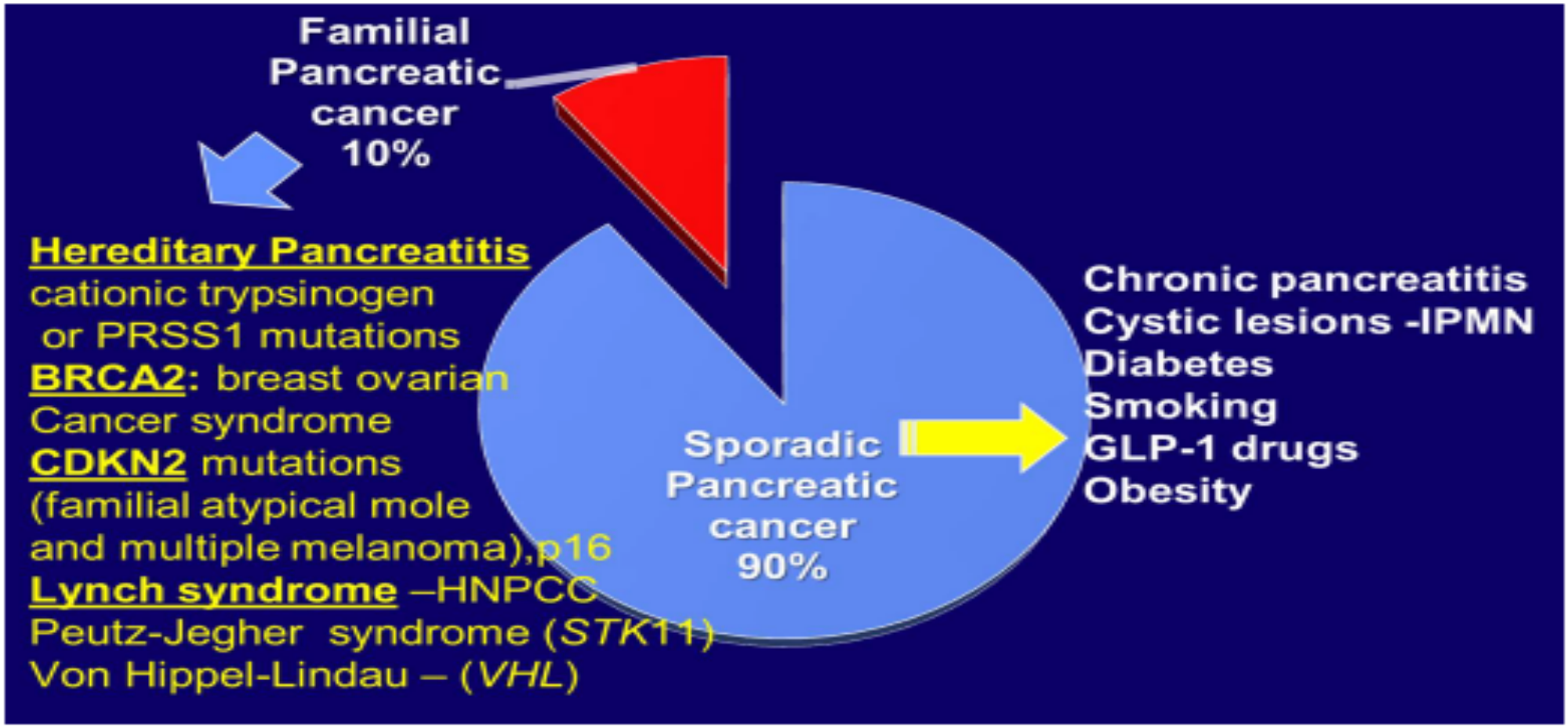
Rahib L et al. Cancer Res 2014;74:2913-2921

Pancreatic cancer prognosis

Pancreatic Cancer: Reasons for Poor Prognosis

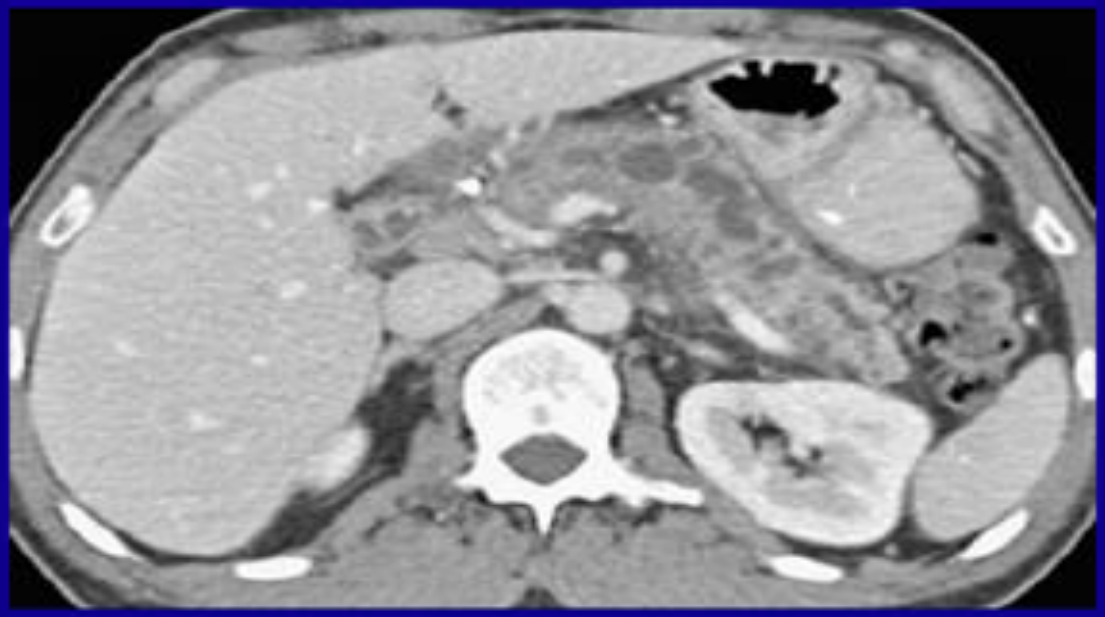
- No methods for early detection
- No screening tests (biomarkers or imaging) for high risk subjects
- Resistant to chemotherapy and immunotherapy due to the dense stroma in tumor microenvironment.
- Treatment is not target specific
- Lacks CD8+T-cells, increase M2 macrophages

Risk factors



IPMN

IPMN



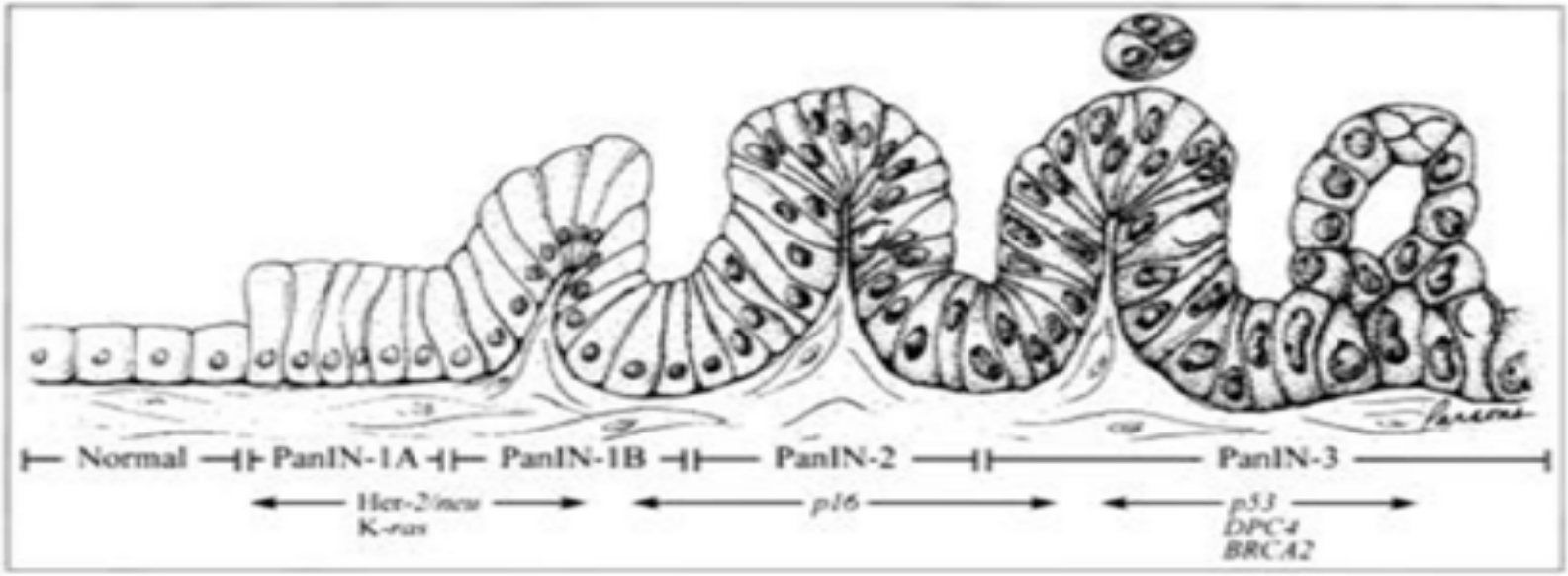
Sendai / Fukuoka criteria for high risk IPMNs. International consensus guidelines 2017 for the management of IPMN and MCN of the pancreas. Pancreatology 2017; 17(5):738-753

Only 10-15% of pancreatic cancer arise from IPMNs or cystic lesions.

PanINs

PanINs

85% of pancreatic cancers arise from a histologic lesion called PanINs

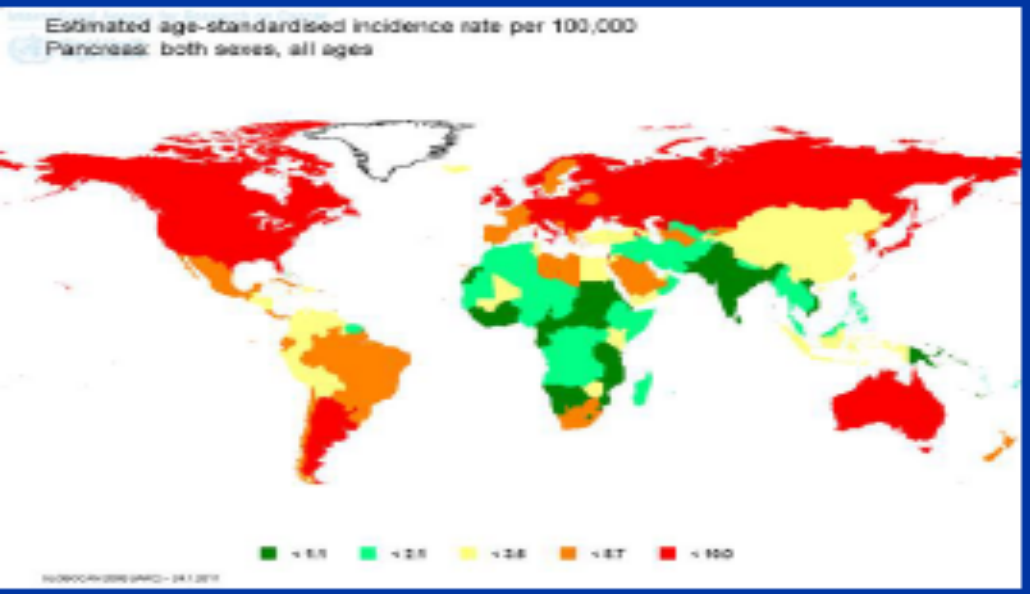


Problem: most people over 70 have PanINs grade 1-2but never progress to cancer
At Stage PanIN3 – may be too late

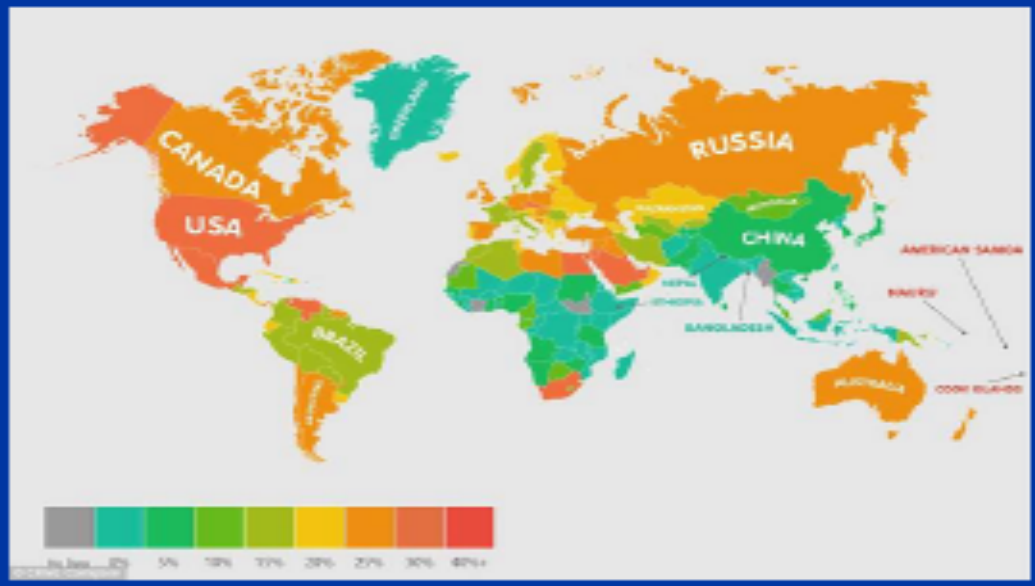
Dietary fat

Pancreatic Cancer and Dietary Fat

There is a direct correlation between dietary fat consumption and the incidence of pancreatic cancer



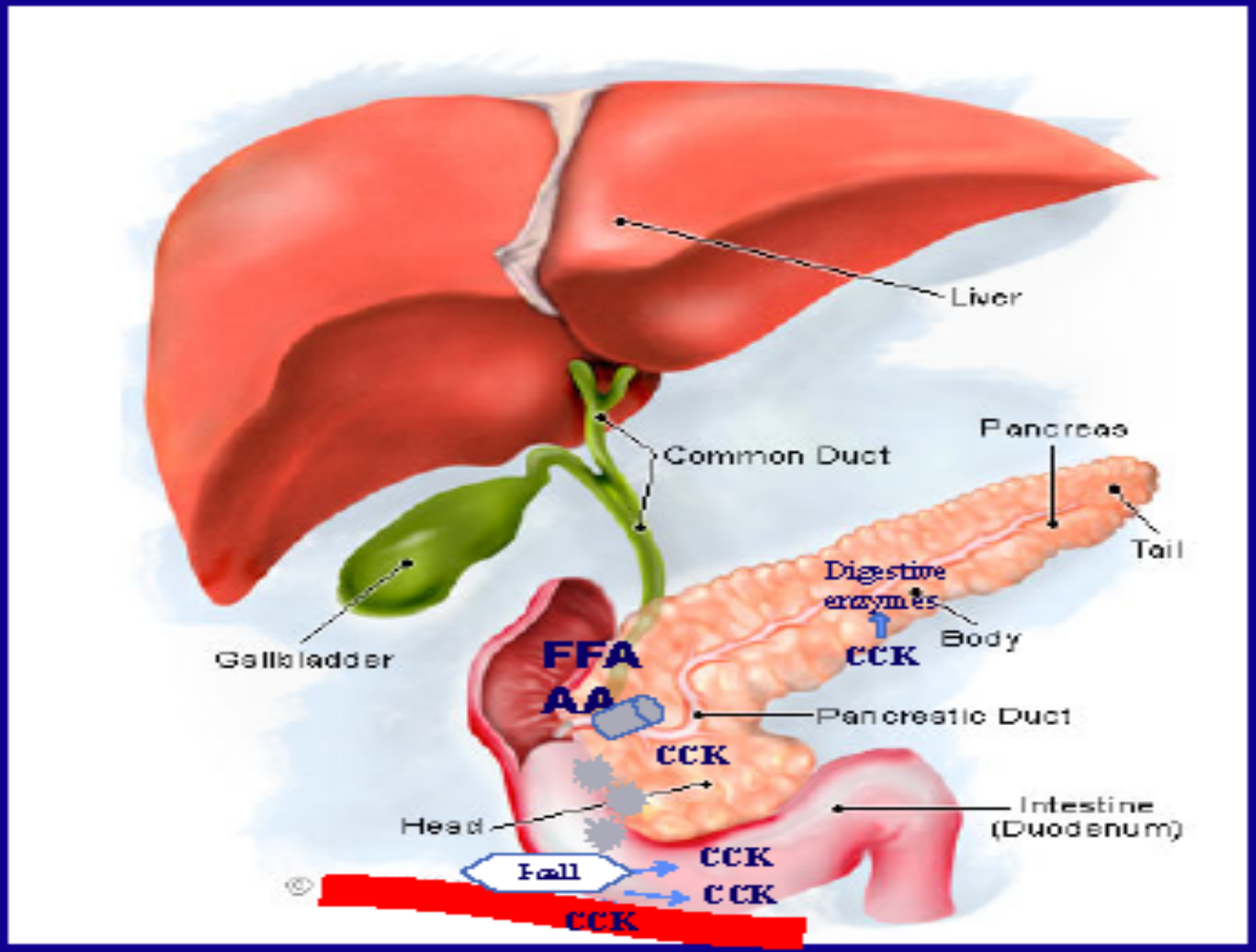
Incidence of Pancreatic cancer World-wide



Dietary fat consumption world-wide

CCK

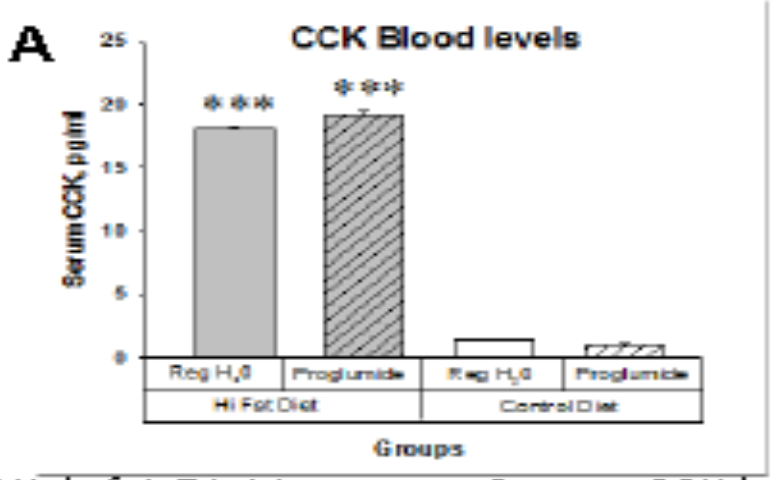
Cholecystokinin: CCK



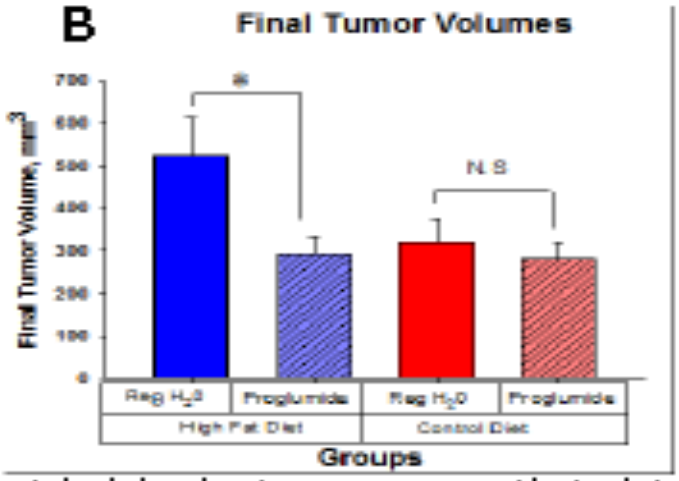
CCK released
By FA chain length
>12

High fat diet

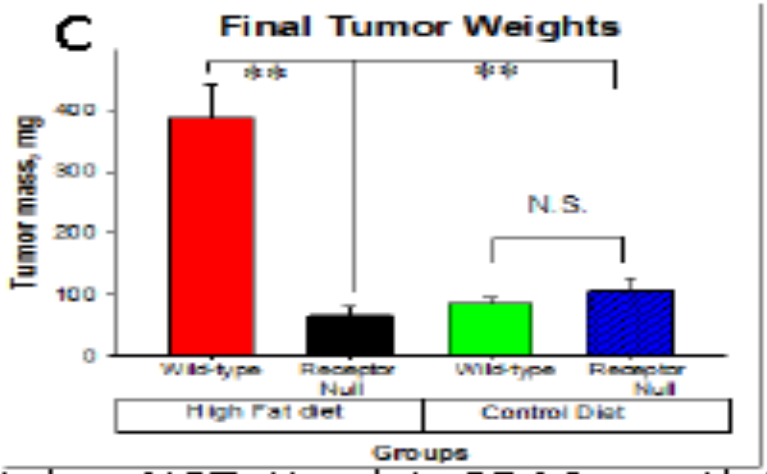
High fat diet stimulates growth of PDAC via the CCK receptor

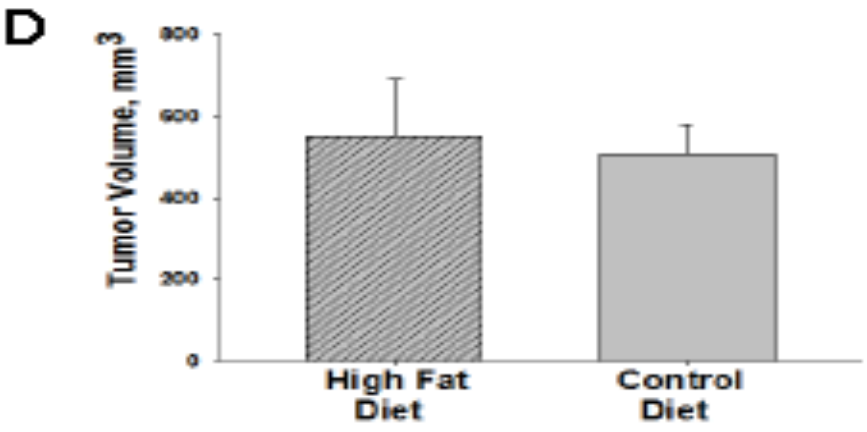


High fat Diet increases Serum CCK levels



Proglumide blocks tumor growth in high fat diet





Fat does NOT stimulate PDAC growth in CCK-receptor-null tumors (C) or CCK peptide-KO mice (D)

CCK receptors

Cholecystokinin Receptors: GPCRs

- CCK-A: Also called CCK-1R
  alimentary tract, gallbladder, pancreas.
  Binds CCK > Gastrin (1,000:1)

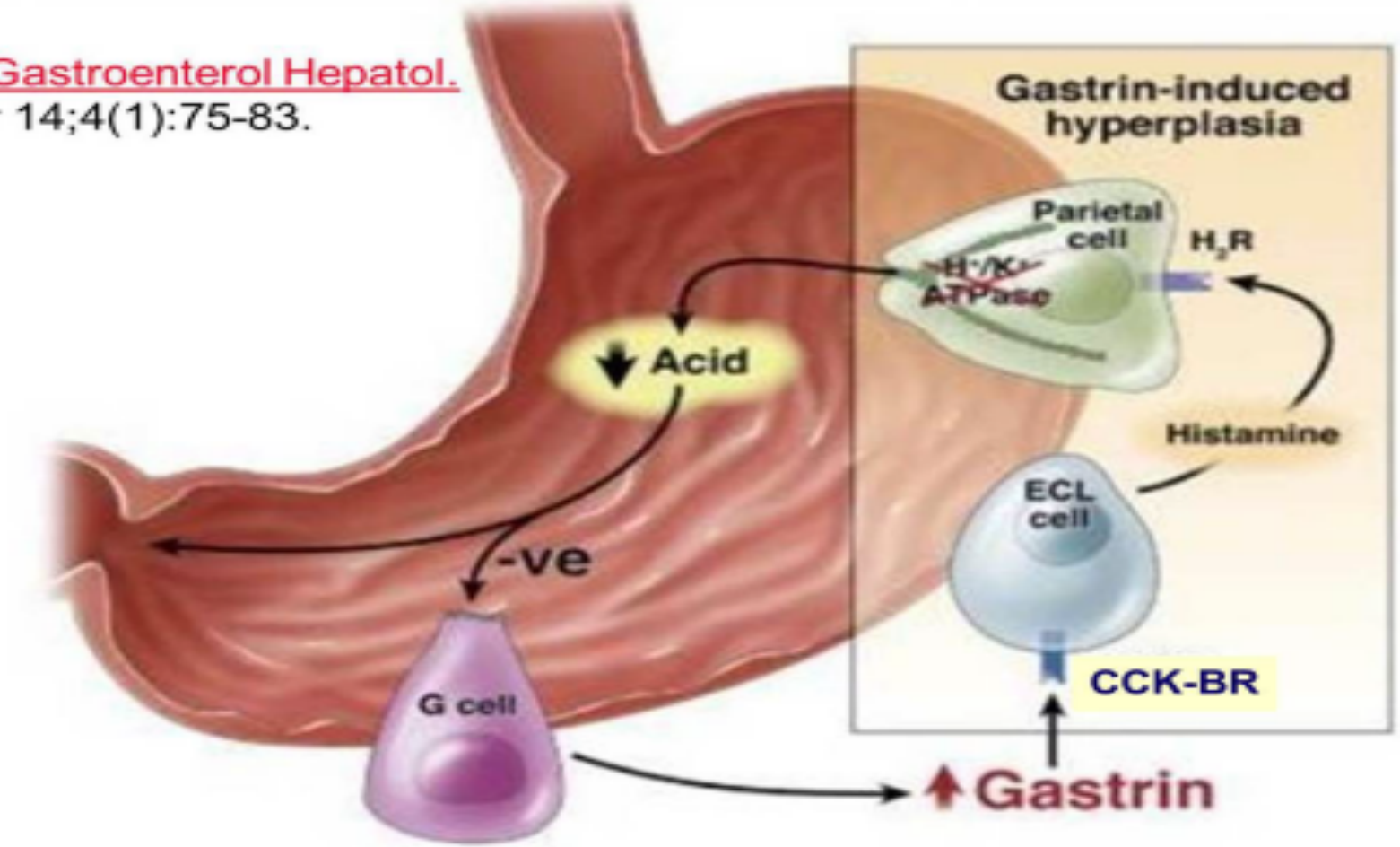
- CCK-B: Also called CCK-2R
  brain, stomach
  Binds CCK = Gastrin (1:1)

- CCK-C: pancreatic cancer, splice variant of CCK-BR; Only found in human cancer, not rodents. Binds Gastrin > CCK (10:1)

Gastrin

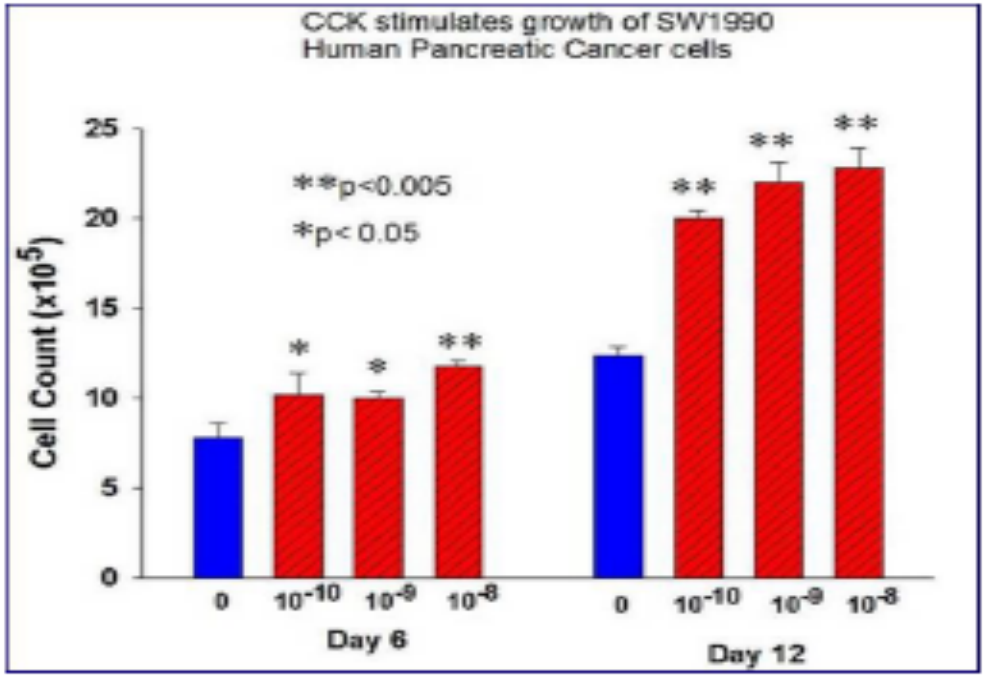
Gastrin Exerts a Powerful Trophic Effect on Enterochromaffin-like cells and Parietal cells

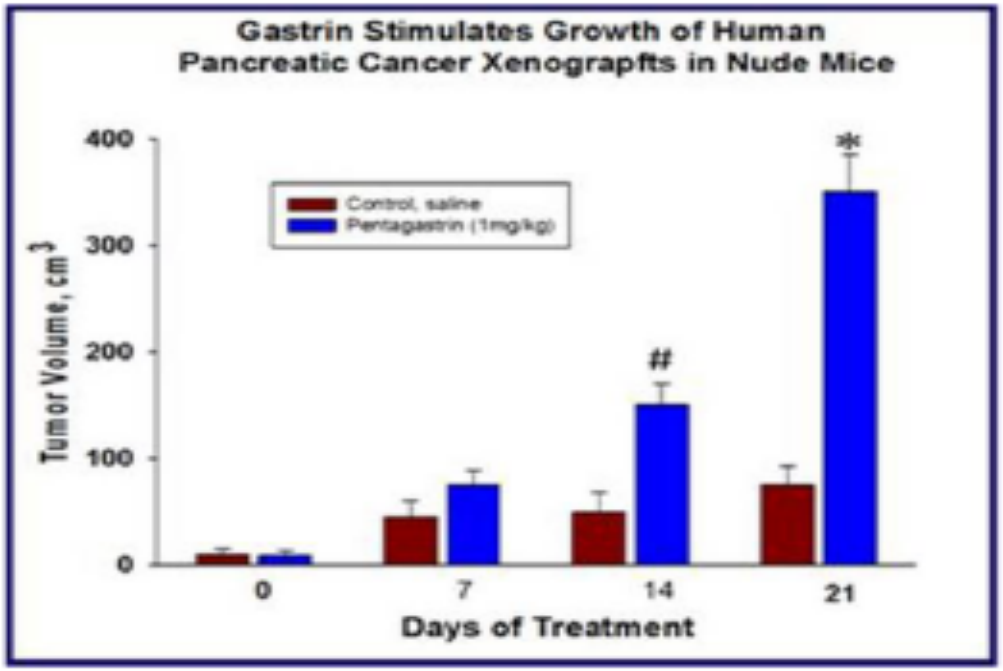
Cell Mol Gastroenterol Hepatol.
2017 Mar 14;4(1):75-83.



Gastrin and growth

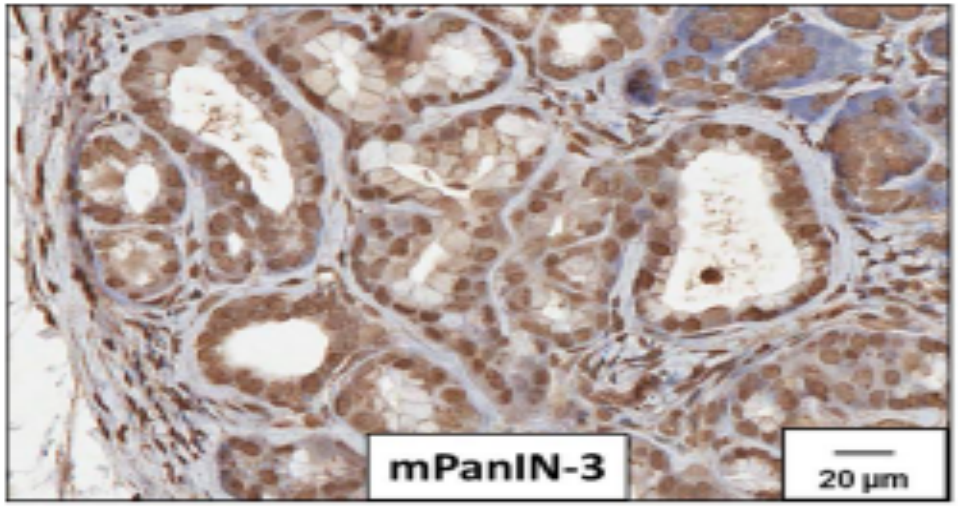
CCK or Gastrin Stimulate Growth of Pancreatic Cancer

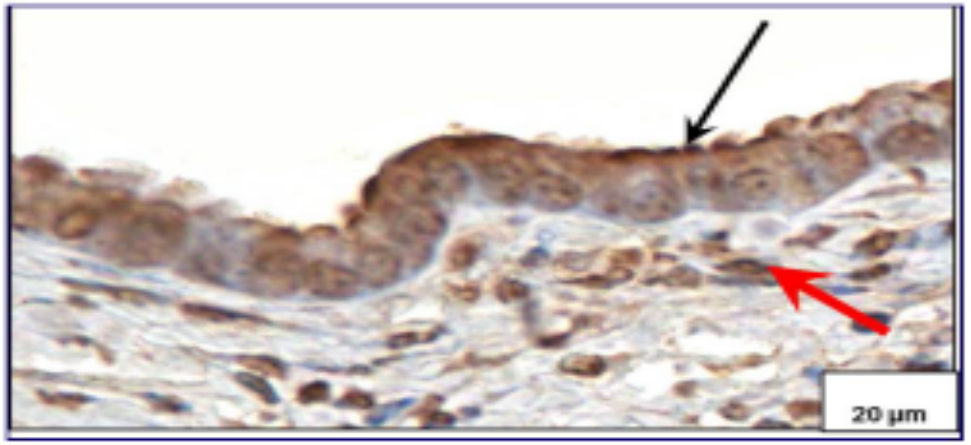


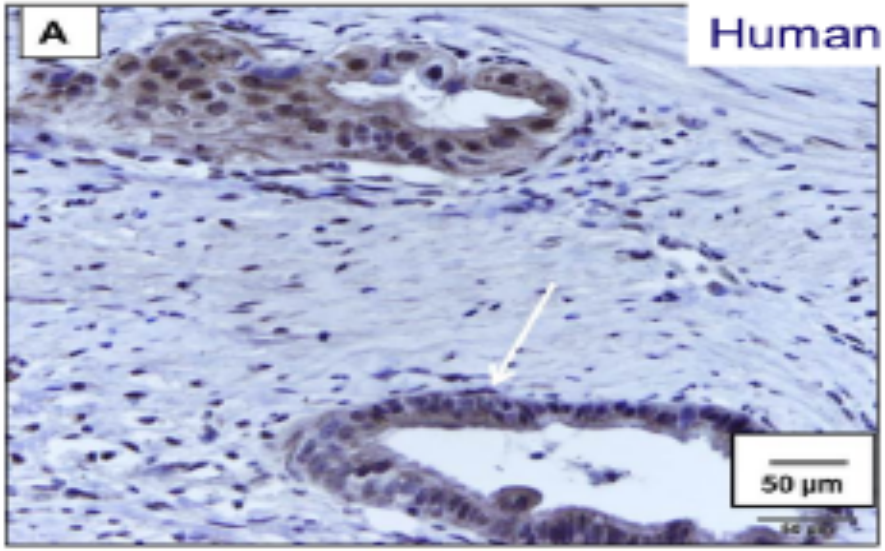


Mouse CCK receptors

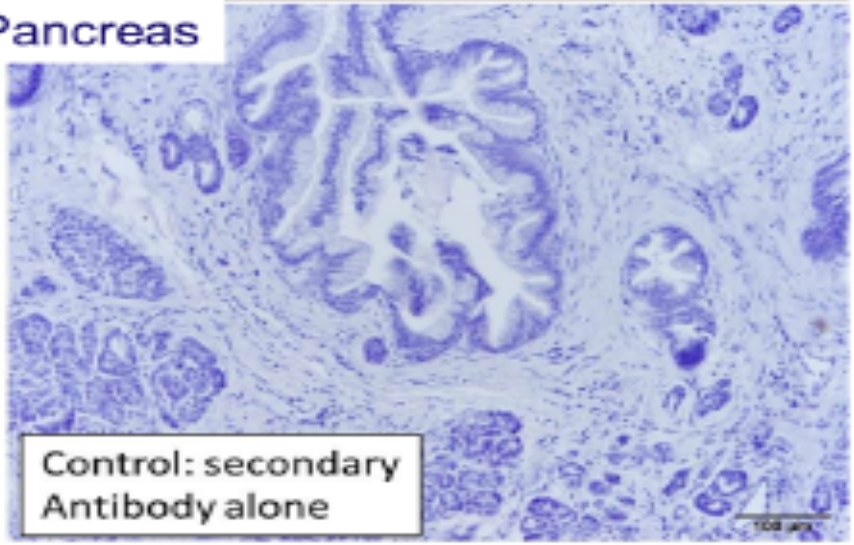
CCK Receptors in Mouse (Pdx1-Cre / LSL-Kras^{G12D})
And human PanIN lesions







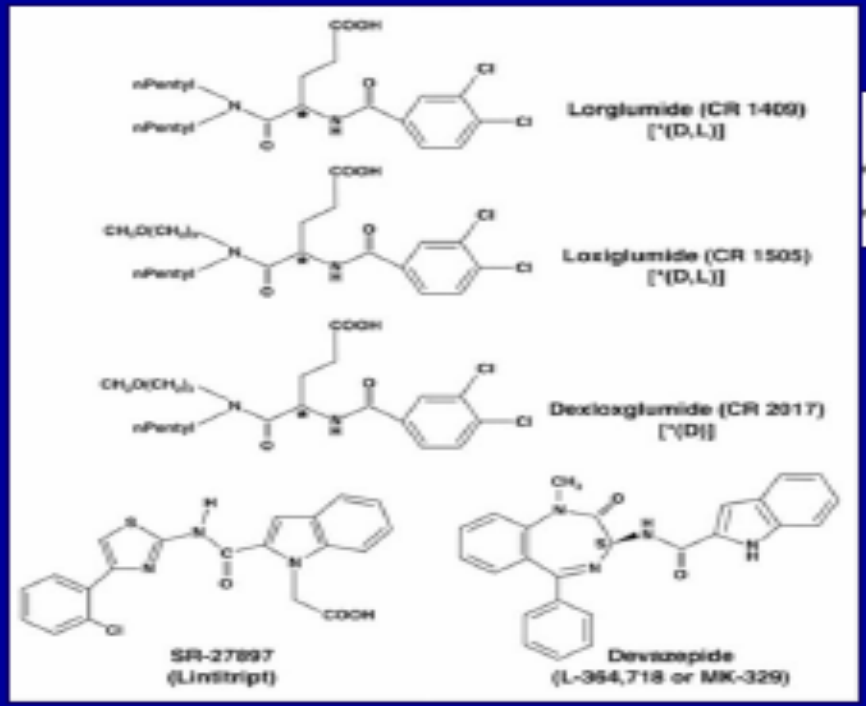
Human Pancreas



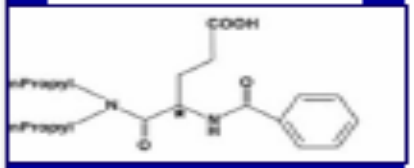
CCKR antagonists

CCK Receptor antagonists

CCK- AAntagonists

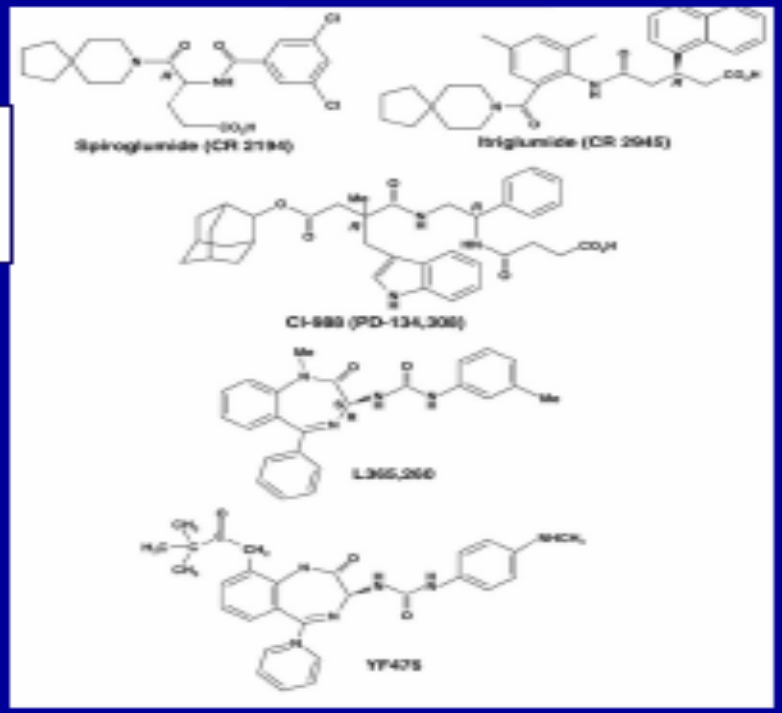


Proglumide
Nonselective



Orally
Bioavailable

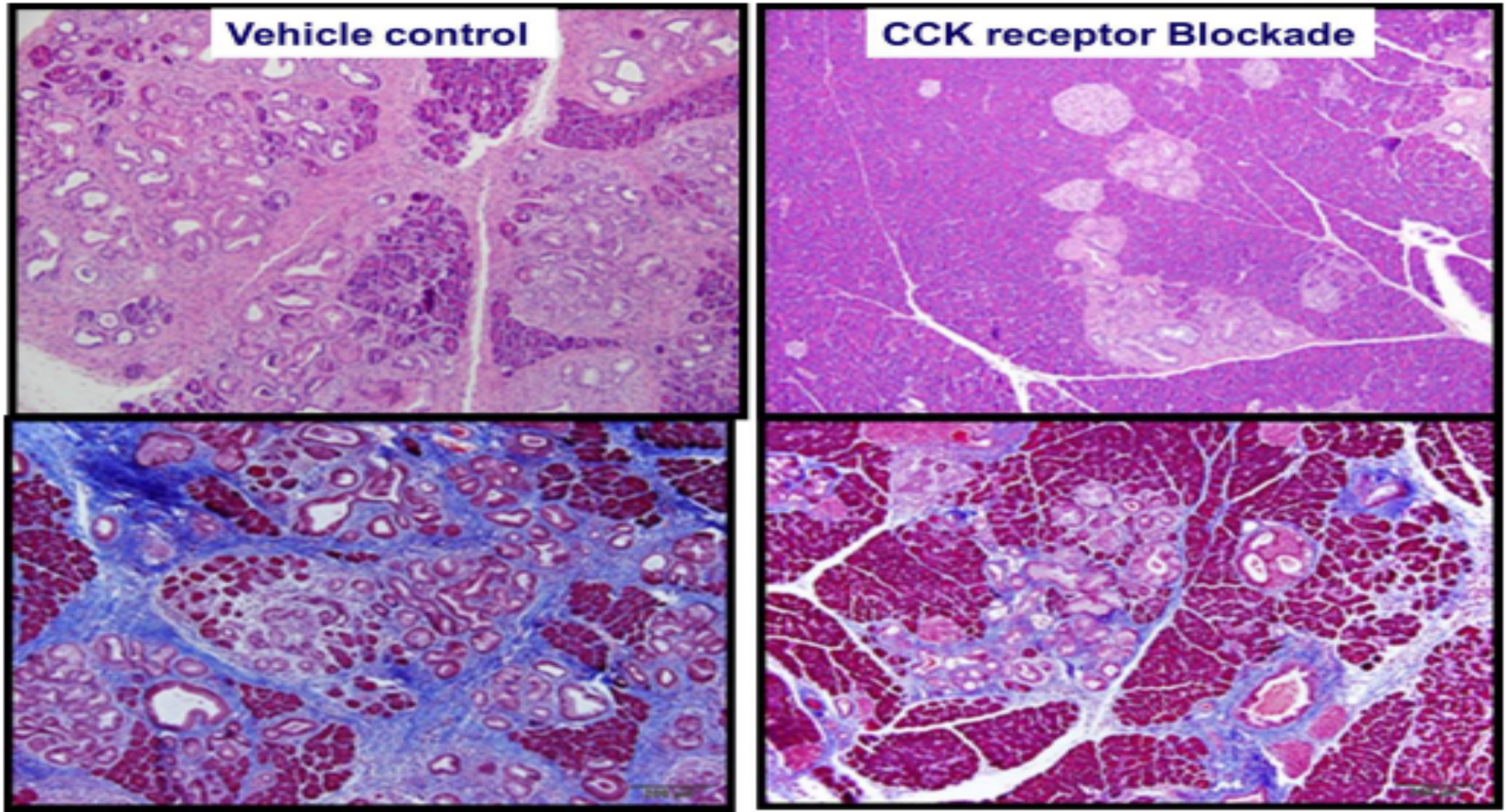
CCK-B antagonists



Berna and Jenson, *Curr Top Med Chem*. 2007

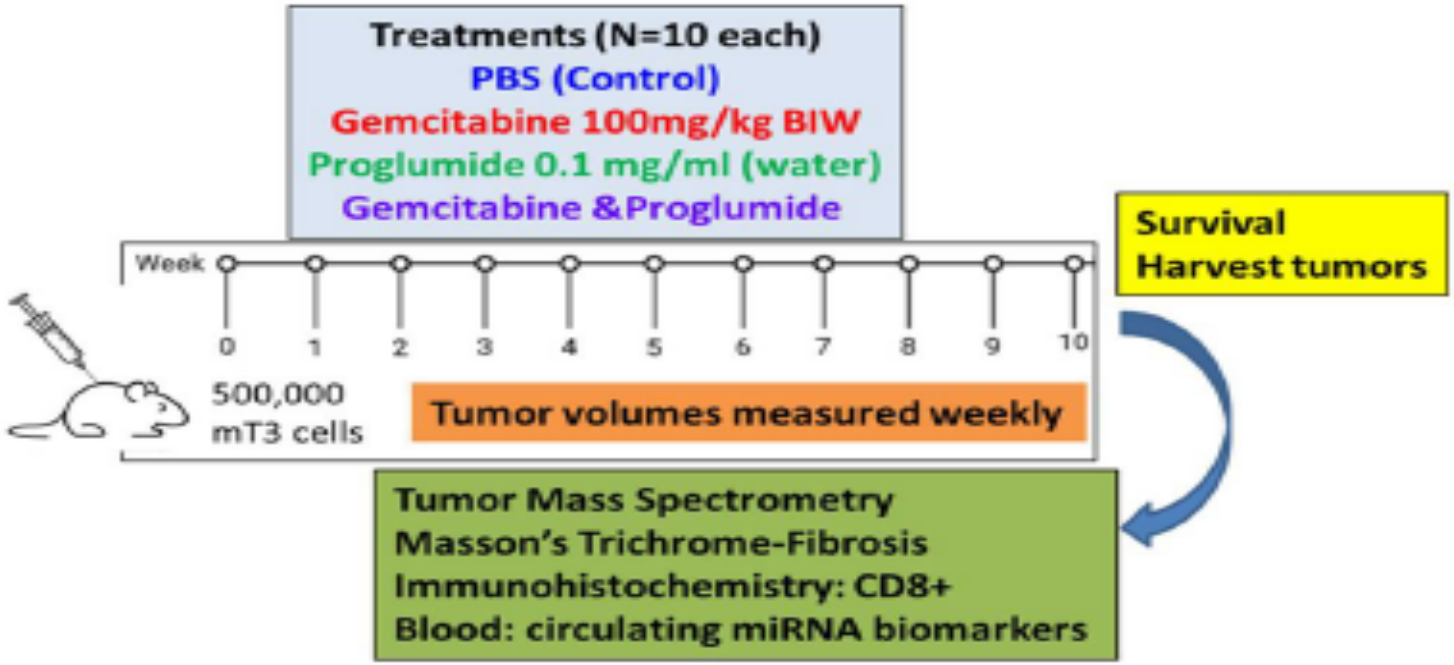
Proglumide blocks progression

Proglumide Blocks PanIN progression and fibrosis



Tumor microenvironment

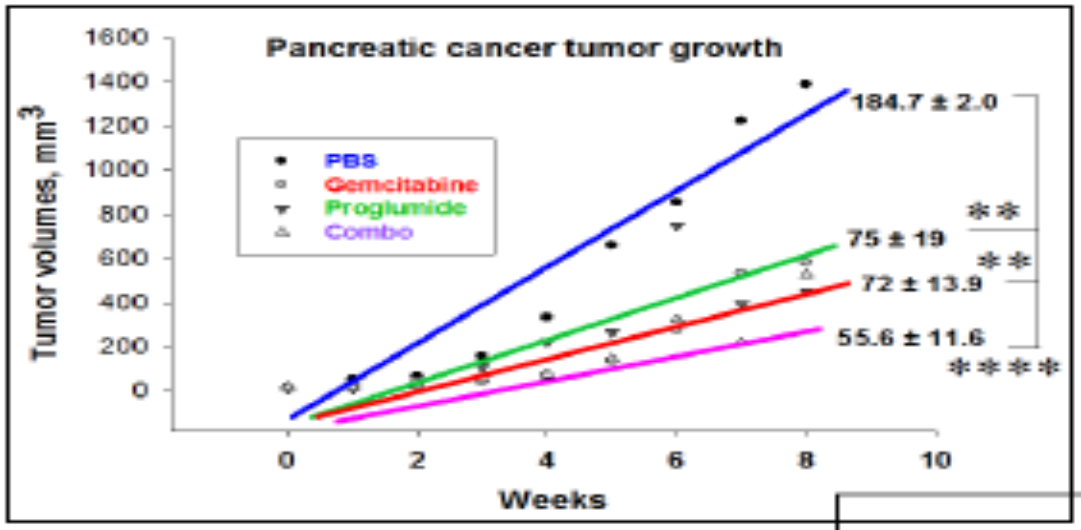
Interruption of CCK-BR signaling alters the Tumor Microenvironment



Although pancreatic cancer cells may respond to chemotherapeutic agents in cell culture, many of these agents are less effective *in vivo*. One reason to explain the lack of efficacy is that most chemotherapeutic agents are not target specific. Another reason why immune checkpoint antibodies and chemotherapeutic agents do not work *in vivo* is the dense fibrosis of the tumor microenvironment (TME) associated with pancreatic cancer that prevents permeation of many agents and prevents penetration of effector T-killer lymphocytes.

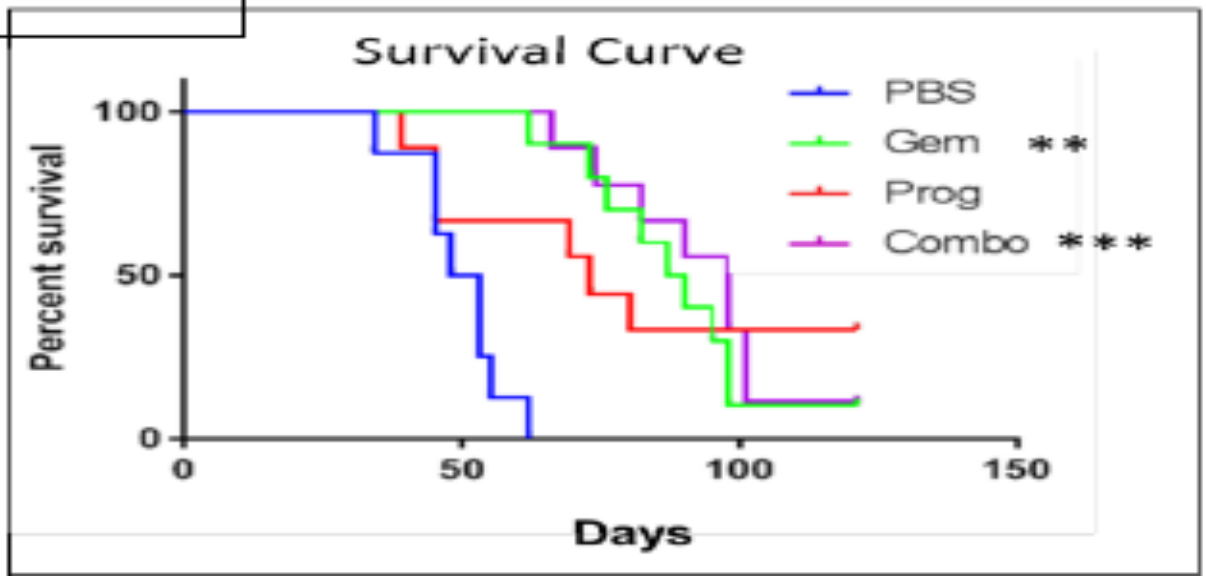
Tumor growth rate

Tumor Growth Rate



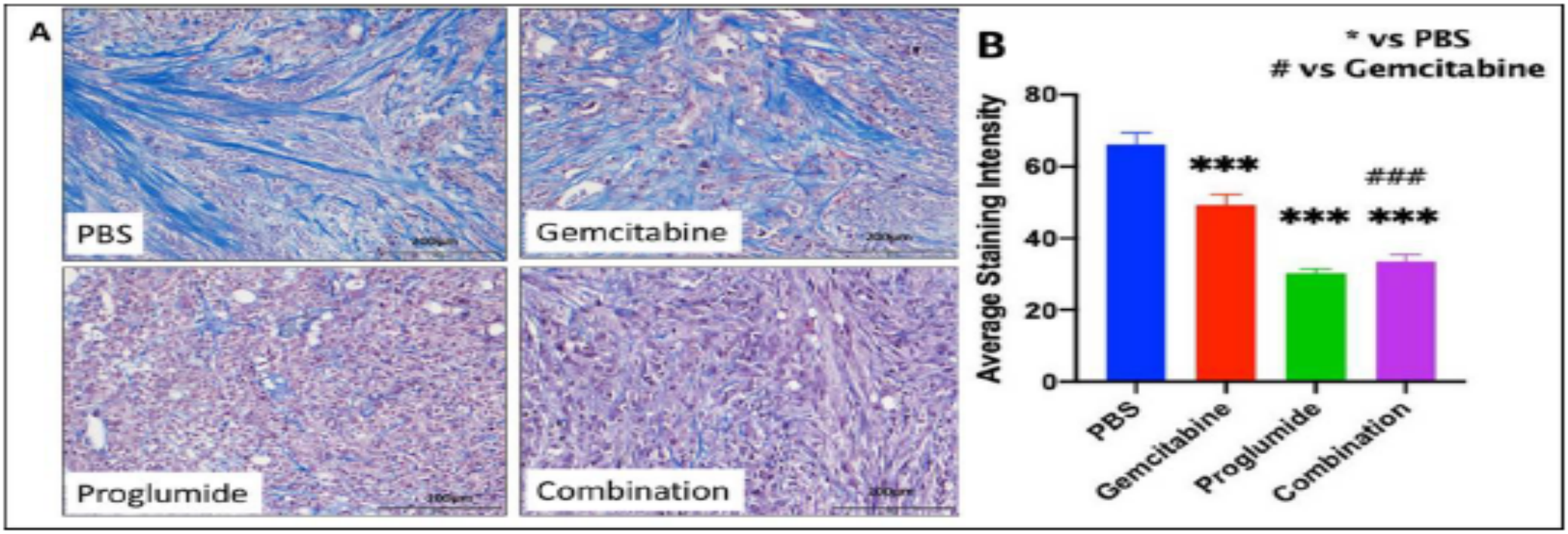
The mice treated with the combination of gemcitabine and proglumide had the slowest growth rate. Significant compared to controls (**p<0.006, ****p<0.0001).

Kaplan Meier Survival Curve
Log Rank was significant for combo compared to controls. ***p<0.001). Proglumide had 3 Complete Responders.

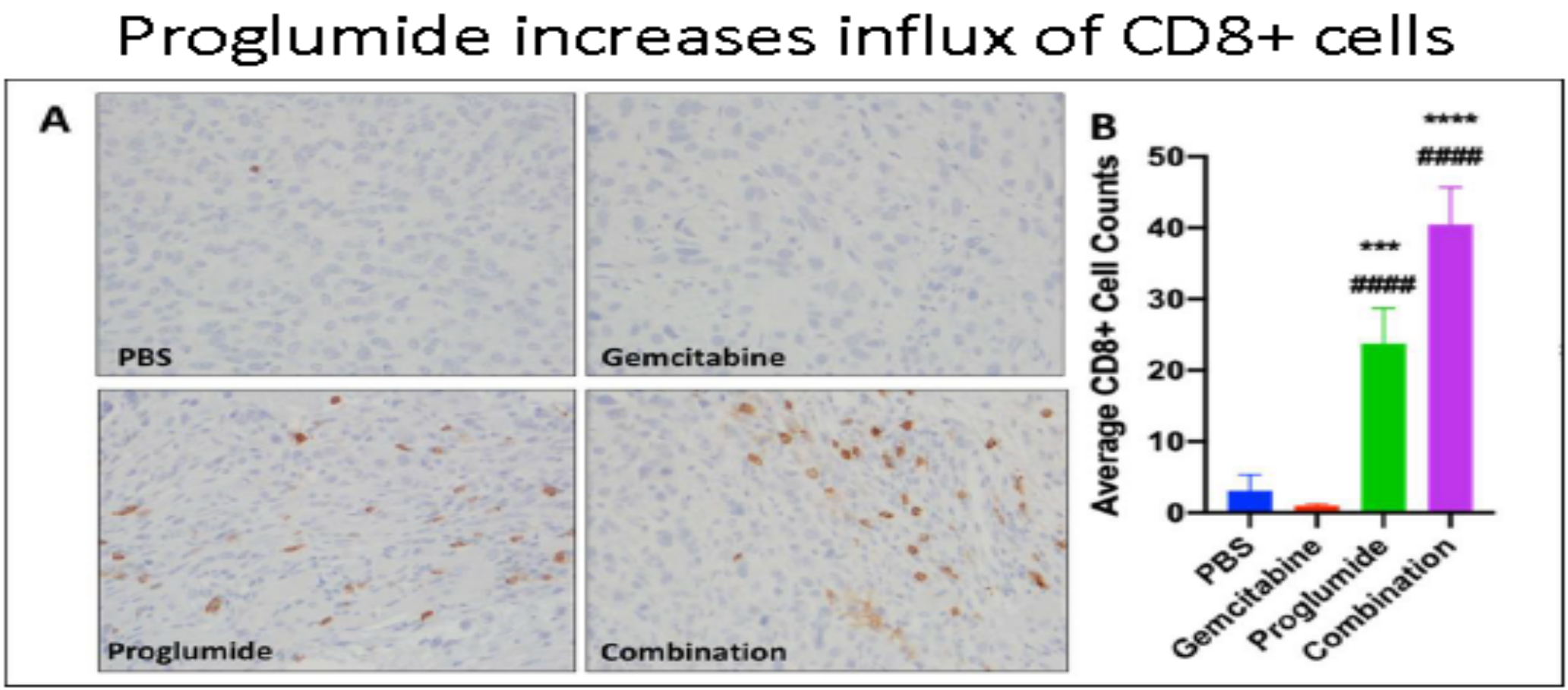


Proglumide reduces fibrosis

Proglumide Decreases Fibrosis in TME

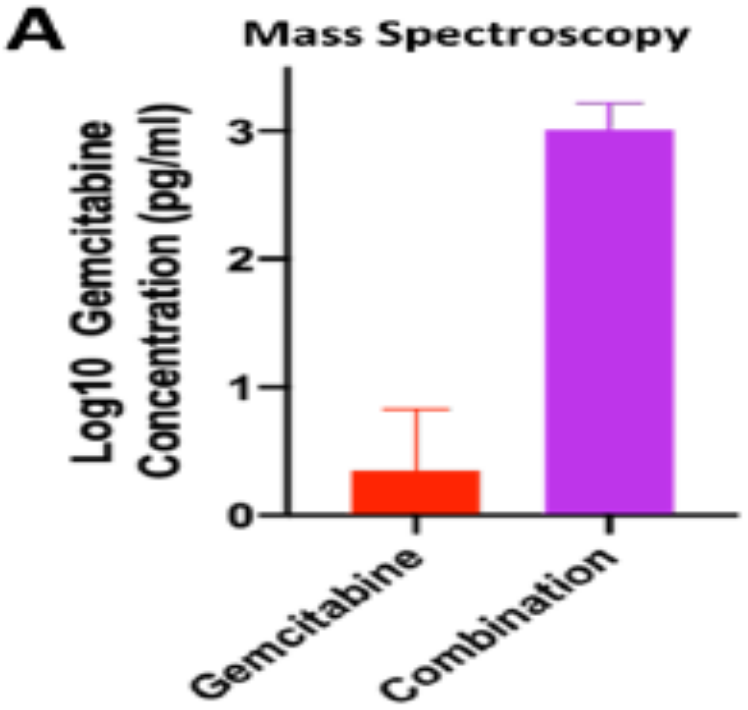


Proglumide increases CD8+ cells



Proglumide increases gemcitabine uptake

Proglumide Increases Gemcitabine Uptake into Tumors



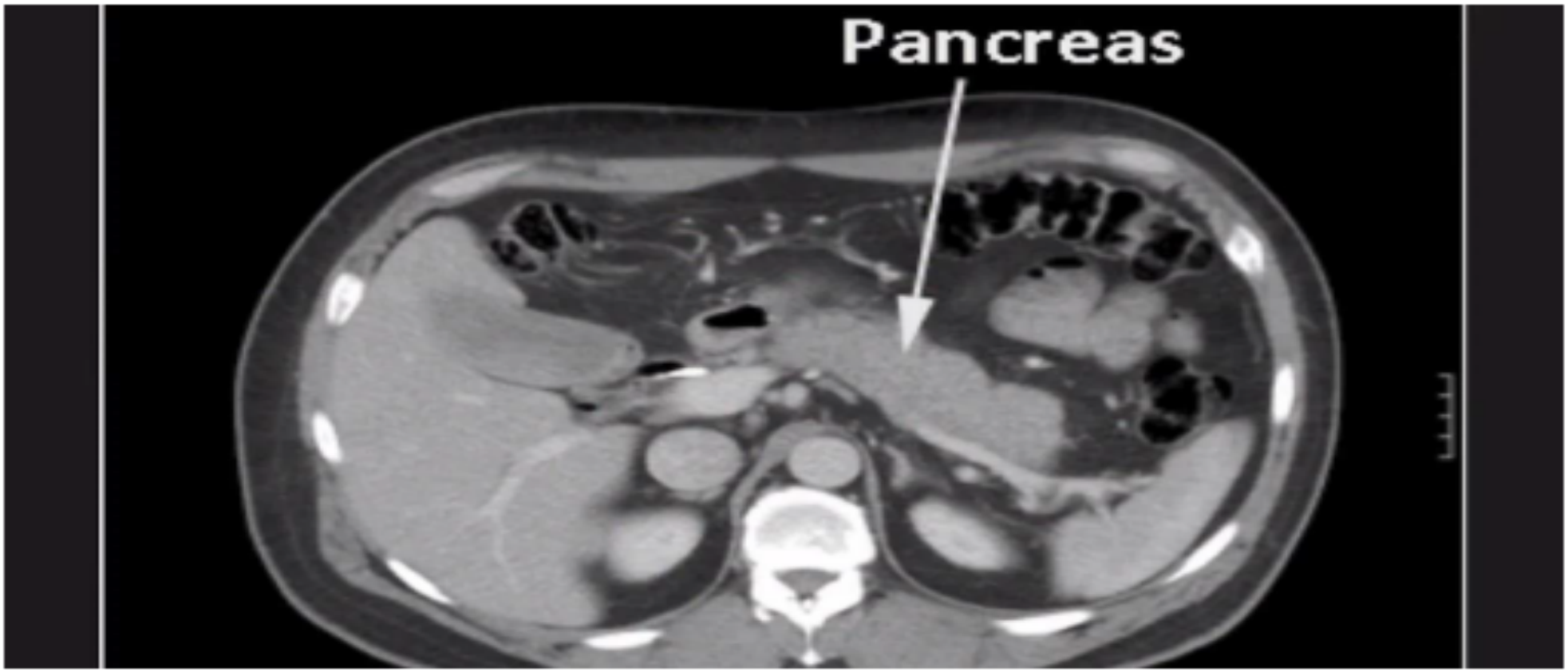
Gemcitabine concentration was increased 8-fold in tumors of mice treated with proglumide.

Proglumide also improved efficacy of immune checkpoint antibodies. Cancer immunology, immunotherapy : 2018; 67(2):195-207 PMID: 29043413

MRI and CT cannot detect PanINs

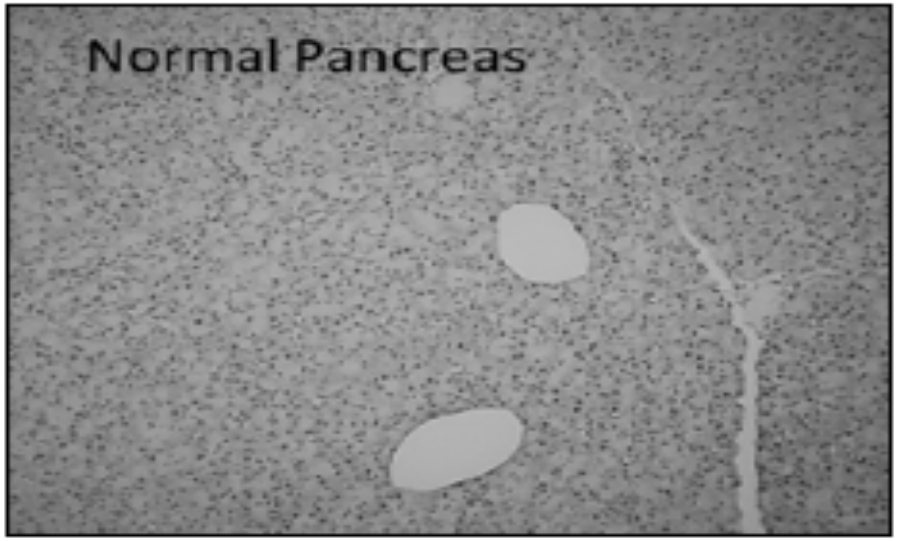
PROBLEM:

MRI & CT Scan cannot detect PanINs

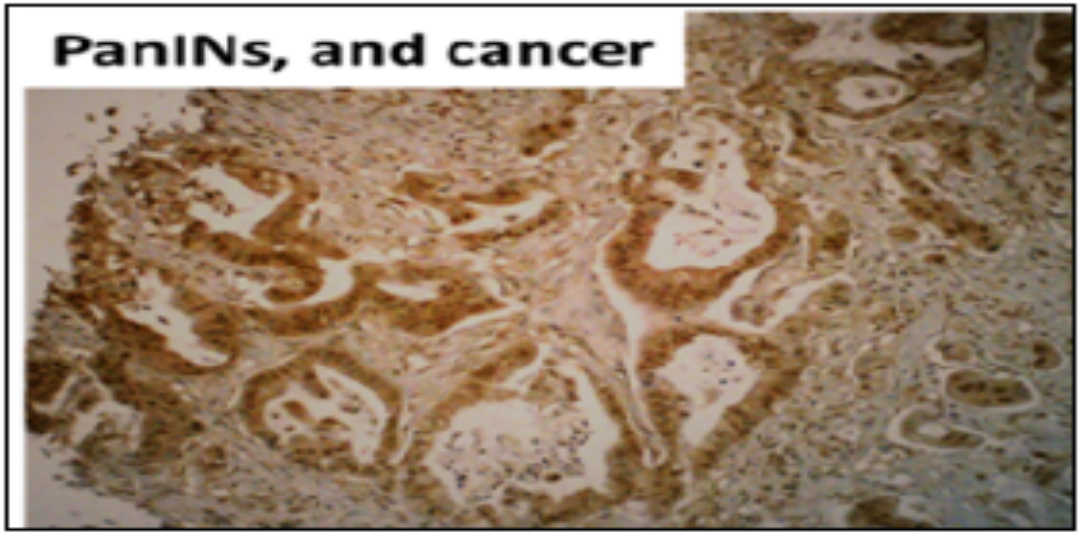


Human pancreas

Human Pancreas



Normal human pancreas reacted with CCK-BR antibody is negative for immunoreactivity.

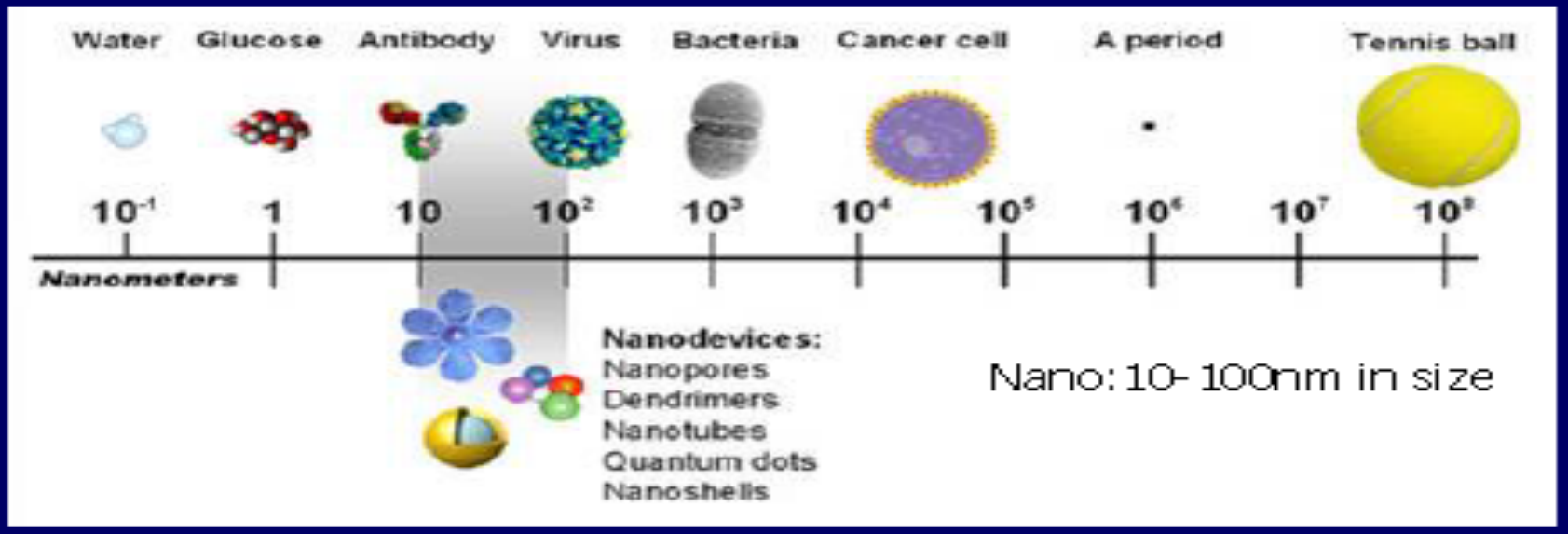


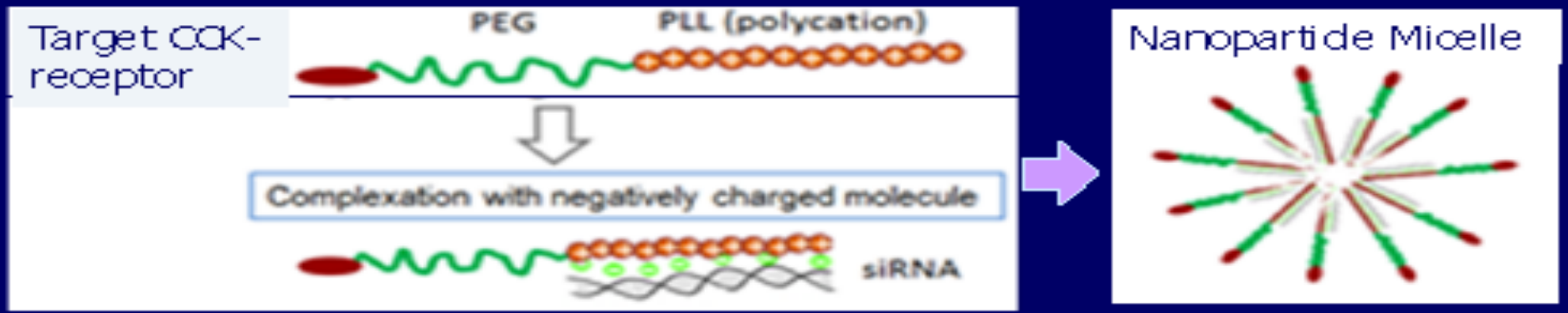
Human PanINs and cancer from a tissue array stains positive for CCK-BR

miR148a activates CCK-BR expression

Nanotechnology and cancer

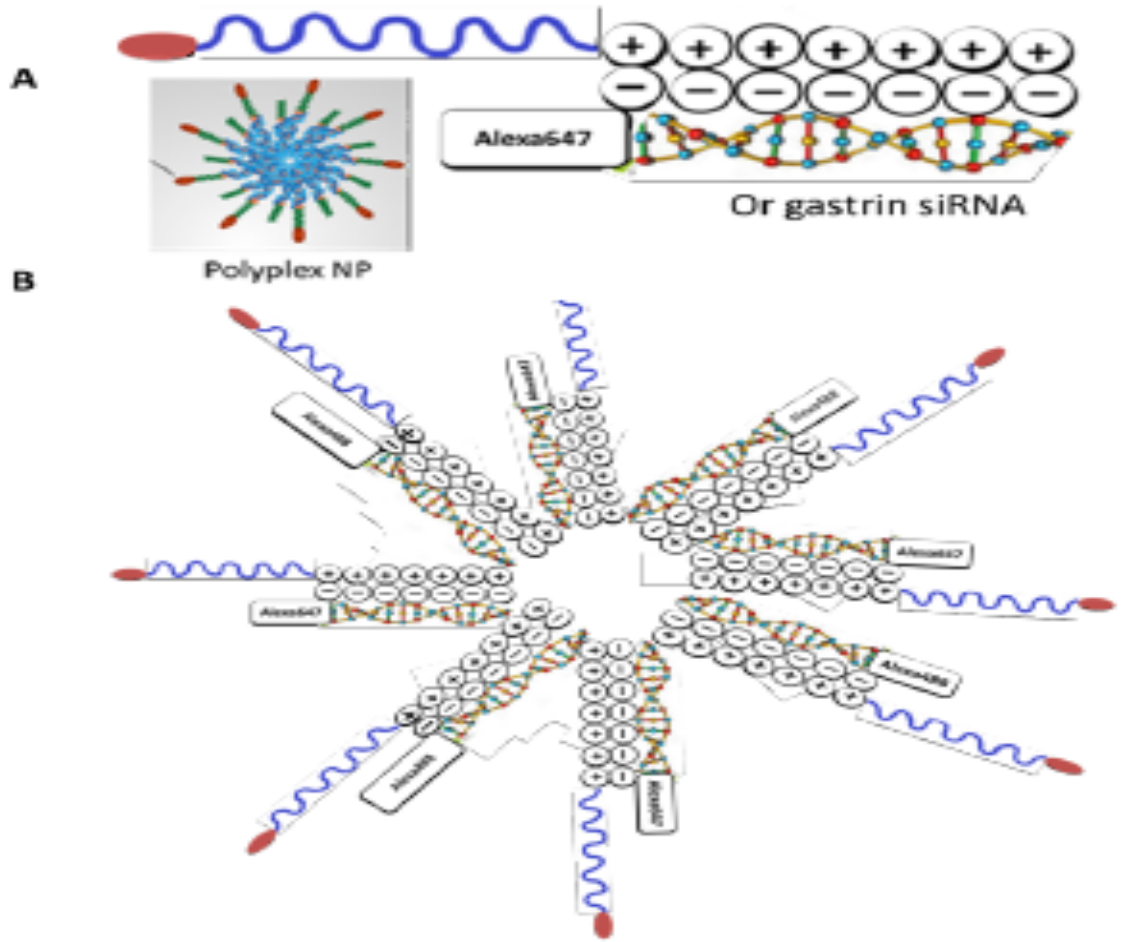
Nanotechnology and Cancer





CCK-BR targeted nanoparticle

Development of a CCK-BR targeted polyplex nanoparticle

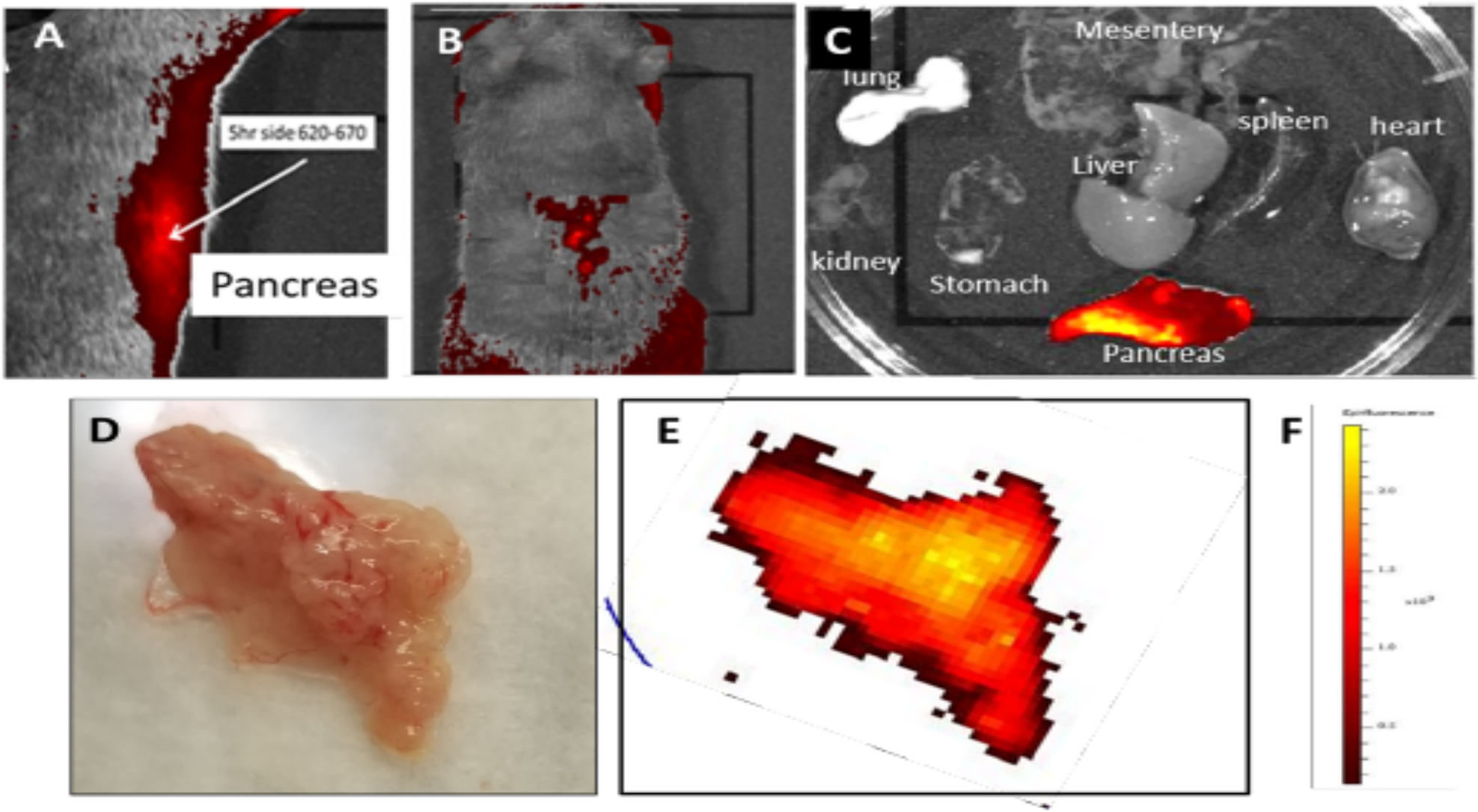


Frederick National Laboratory for Cancer Research

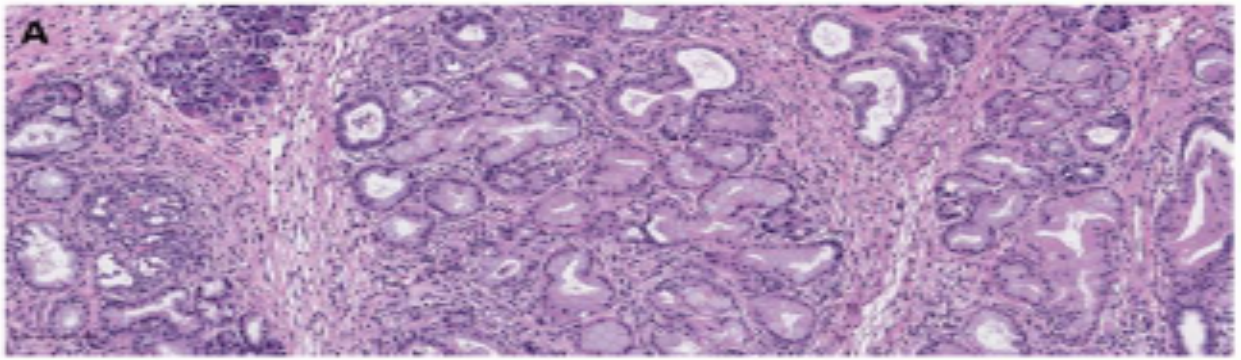
Drs. Steve Stern
And Elijah Edmondson

Imaging machine

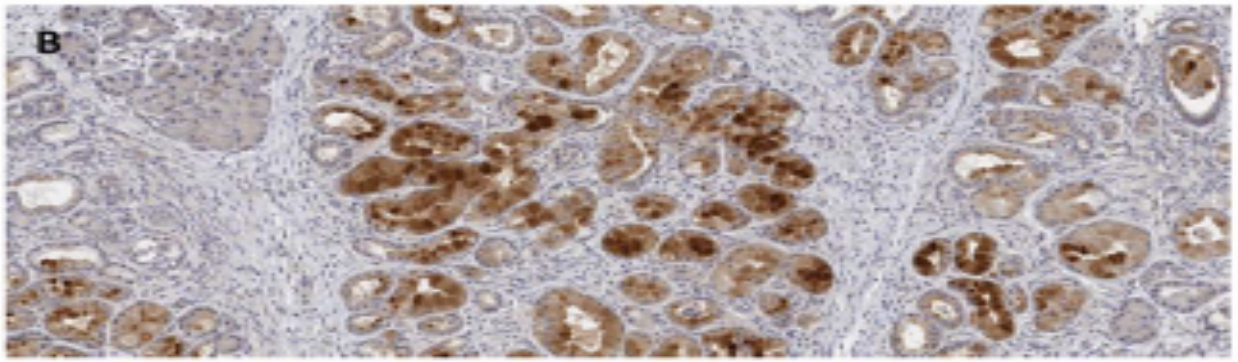
Imaging of mice and organs ex vivo in an IVIS machine for Alexa647 uptake



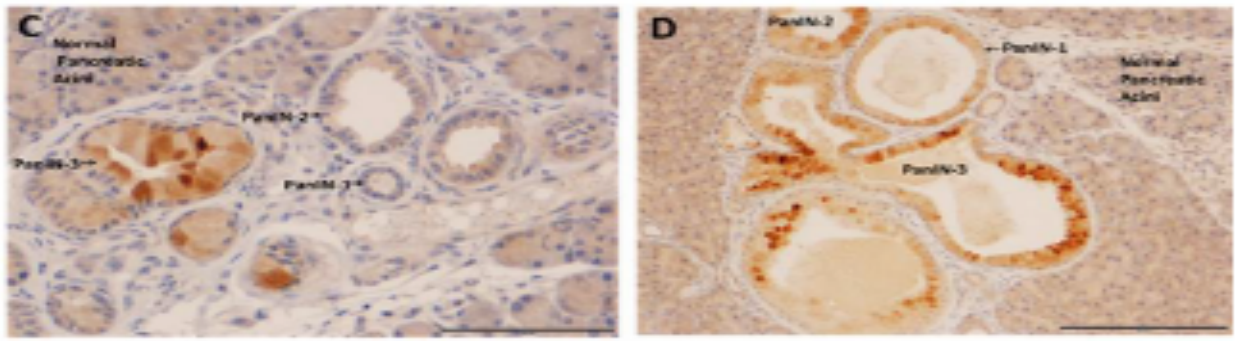
Immunocytochemistry



H&E



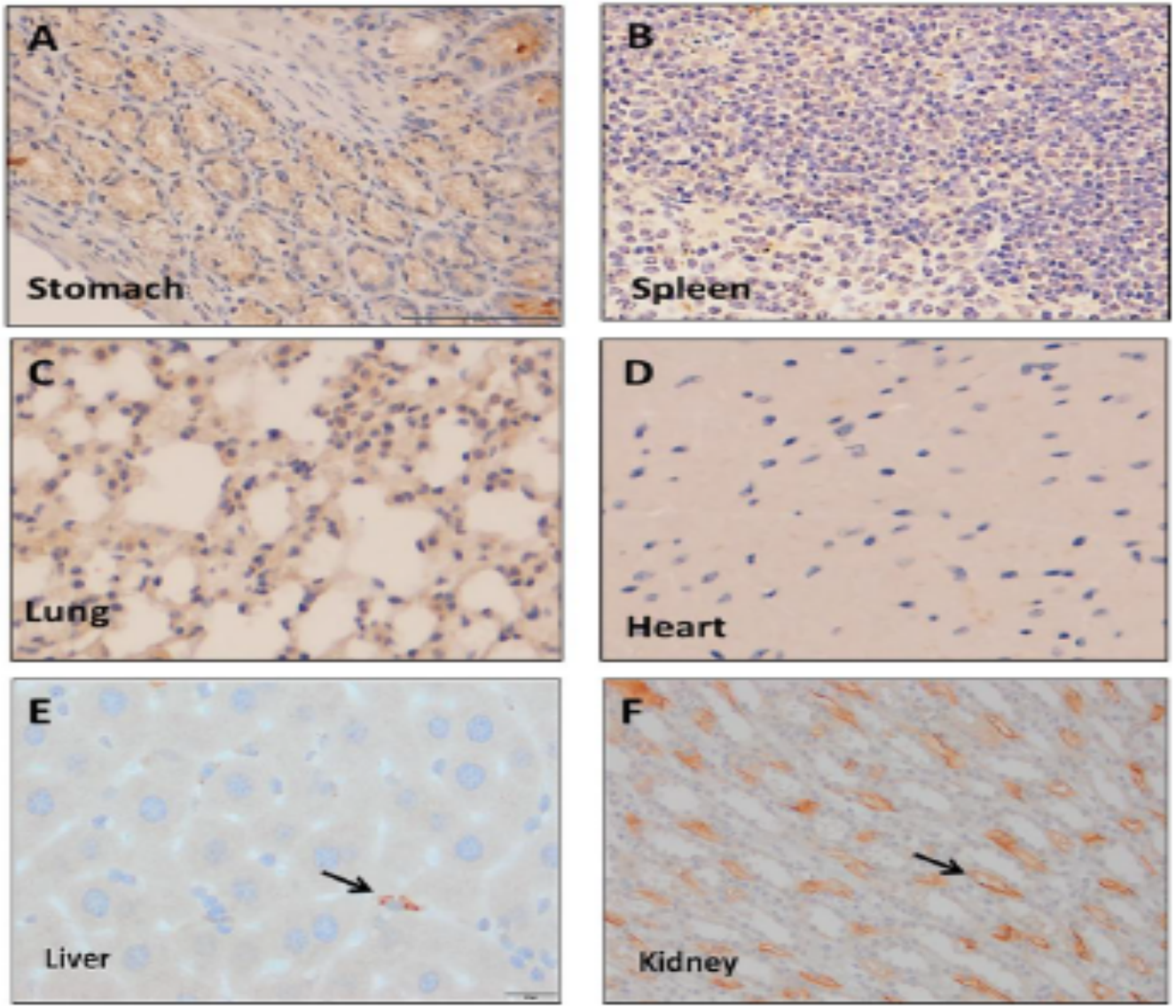
IHC PEG



IHC+ PEG
PanIN3 lesions

Immunocytochemistry

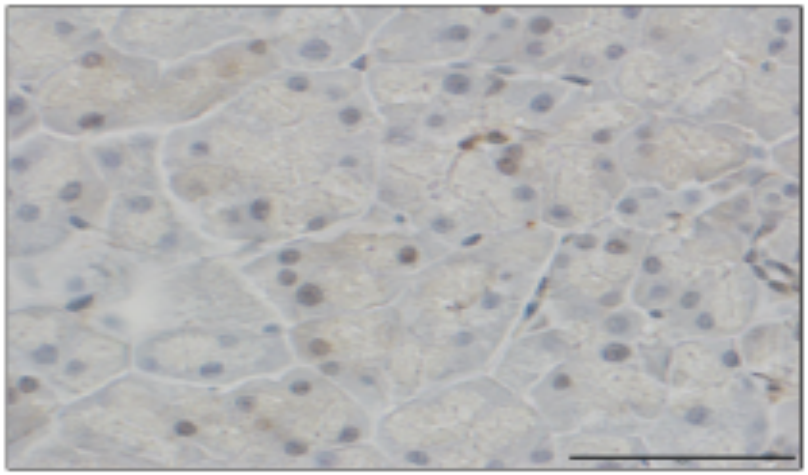
No off-Target effect
Minimal polyplex binding to other tissues



Immunocytochemistry scores

	Normal Pancreas		PanINs		Liver		Kidney		Heart		Stomach	
Sample	% positive	H-Score	% positive	H-Score	% positive	H-Score	% positive	H-Score	% positive	H-Score	% positive	H-Score
ID98	0.01	0.01	9.33	21.82	0	0	0.02	0.02	0.06	0.07	0	0
ID101	0	0	18.48	31.39	0.02	0.02	0.07	0.13	0	0.01	0	0
ID114	0	0	31.72	58.32	0.01	0.01	0.01	0.01	0	0	0	0

Immunoreactivity H-scores from other organs were negligible.
Only PanIN lesions had immunoreactivity consistent with nanoparticle

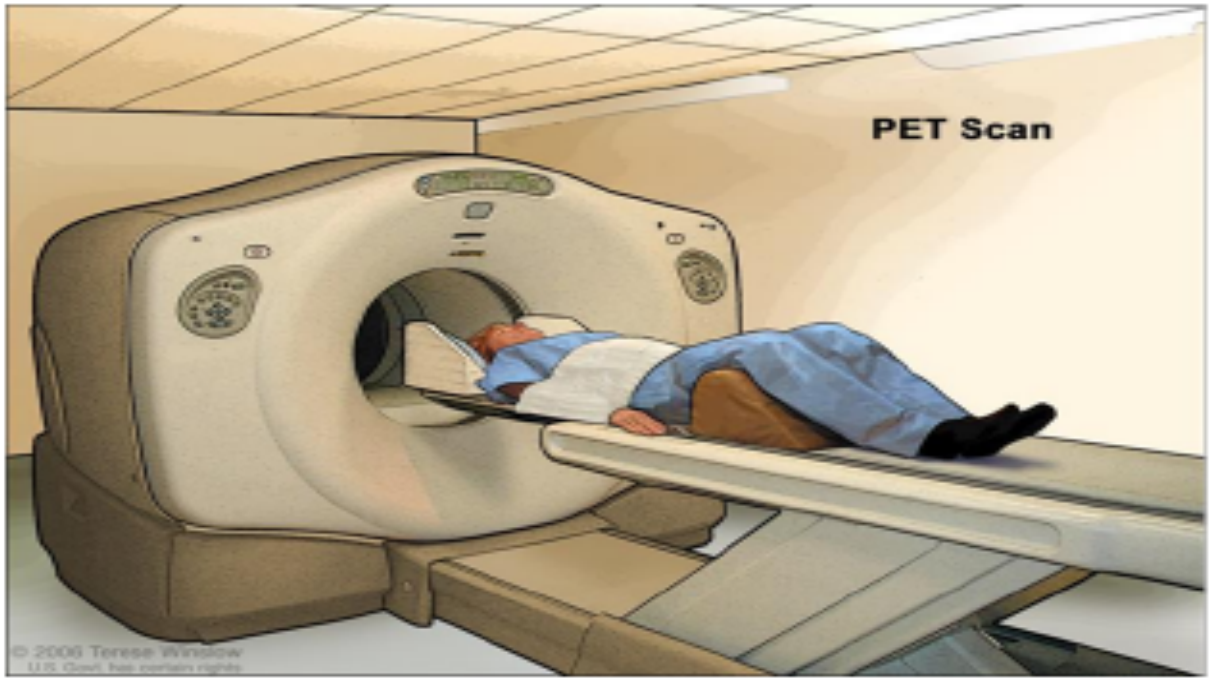


Normal mouse pancreas acinar cells. IHC for normal mouse tissue reacted with anti-PEG did not reveal any immunoreactivity. Bar = 50µm.

Plans to develop an imaging tool for high risk patients to detect early PDAC or high grade PanINs

Nanoimaging

Nano-imaging for early detection

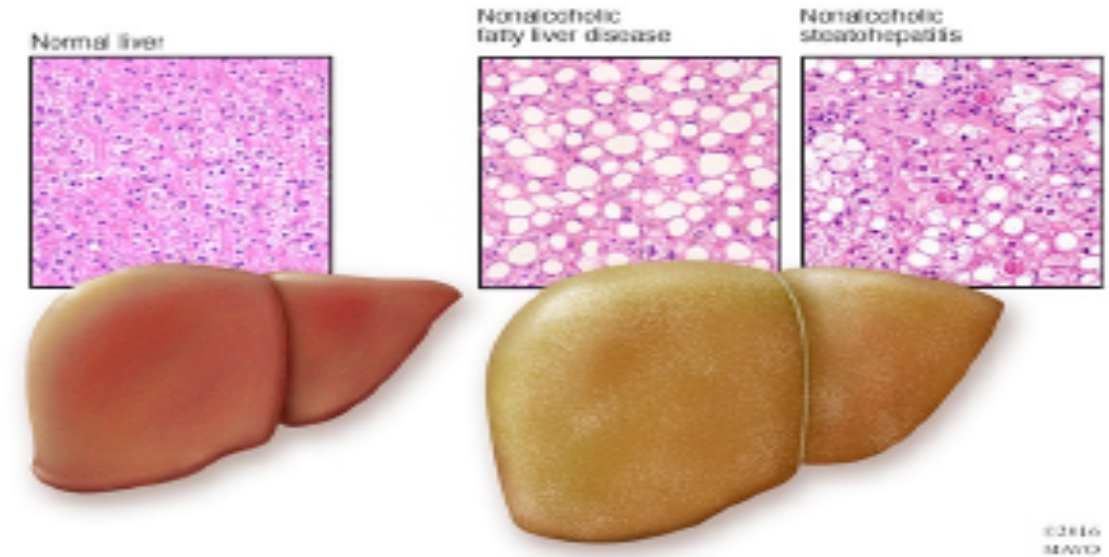


Develop the CCK-targeted nanoparticle with fluorescent probe for an imaging test for early diagnosis

Liver cancer

Targeting the CCK- receptor with Proglumide in Liver

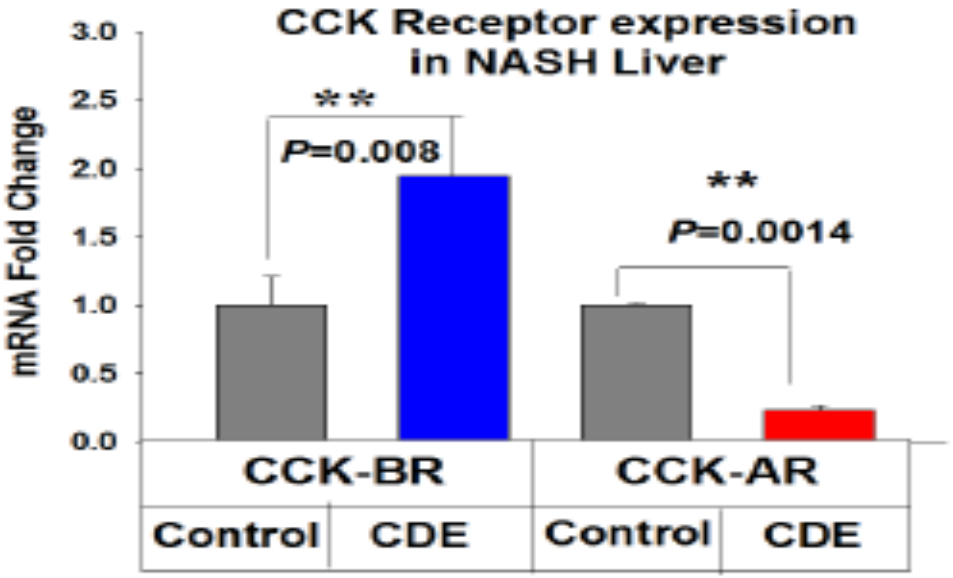
- Non-alcoholic Steatohepatitis (NASH) is a type of Non-Alcoholic Fatty Liver Disease (NAFLD)
- U.S. incidence 15+M, 5% of U.S. Adults
- The histologic hallmarks of NASH include liver cell damage, inflammation, fat in the liver (steatosis) and fibrosis.

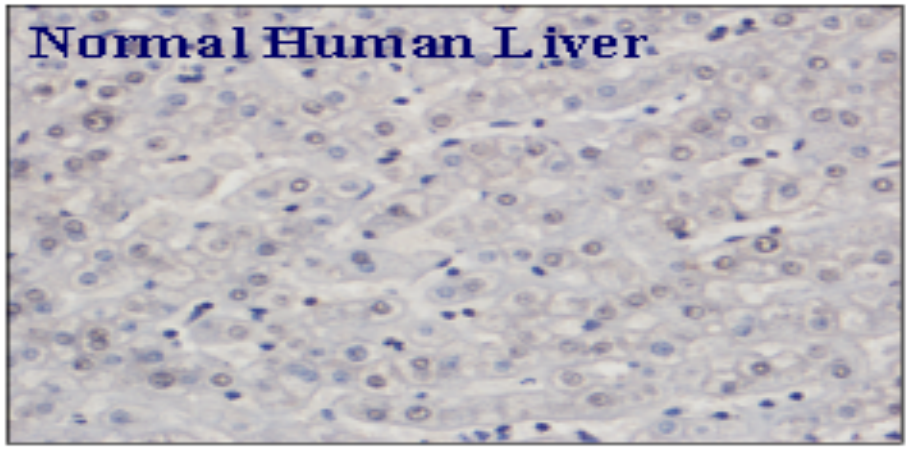


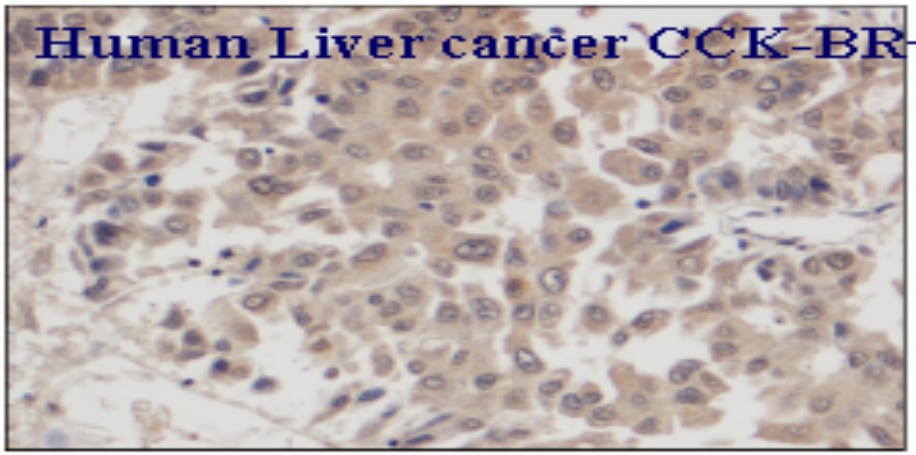
Fibrosis in NASH increases risk of hepatocellular cancer

High fat diet

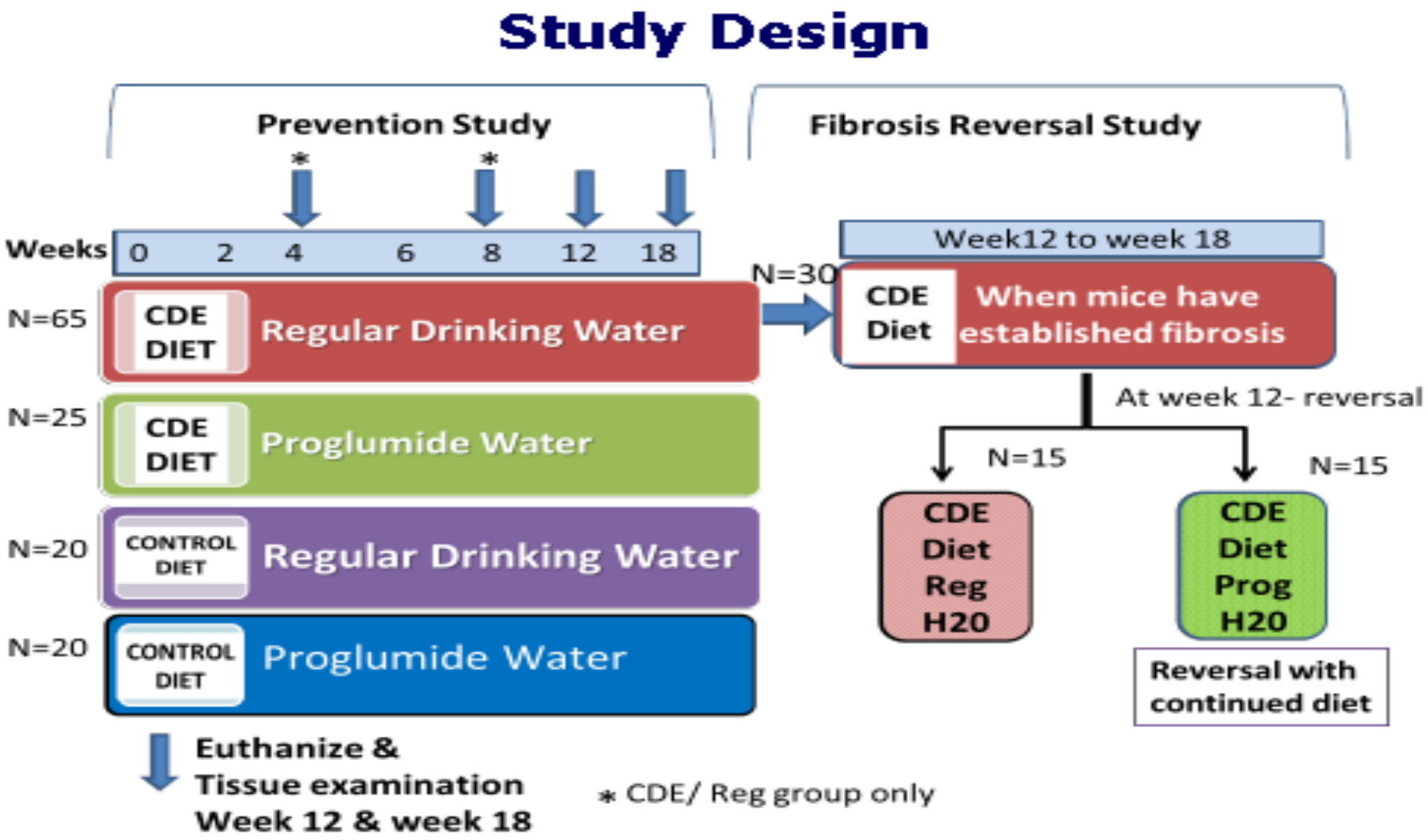
High Fat Diet increases CCK-BR Expression





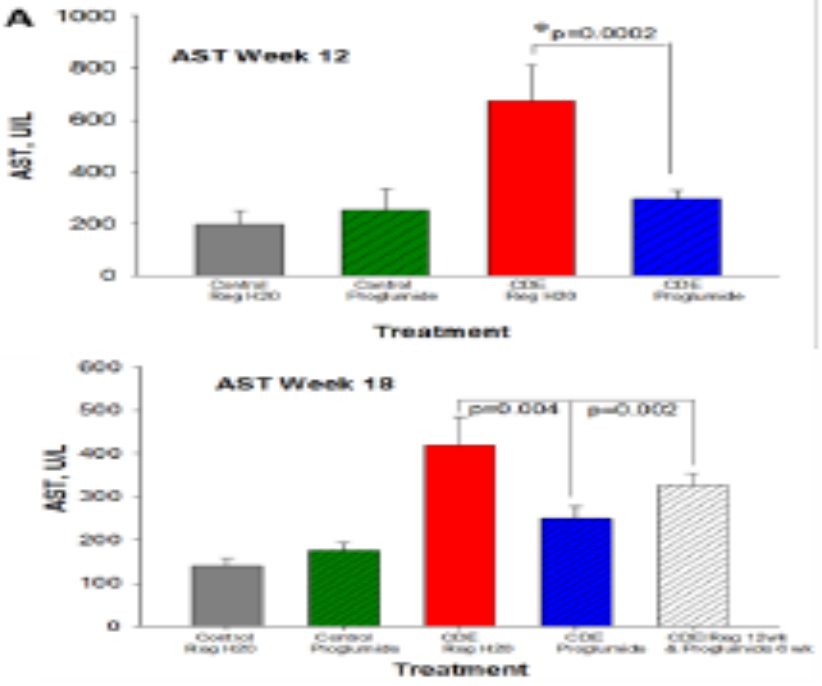


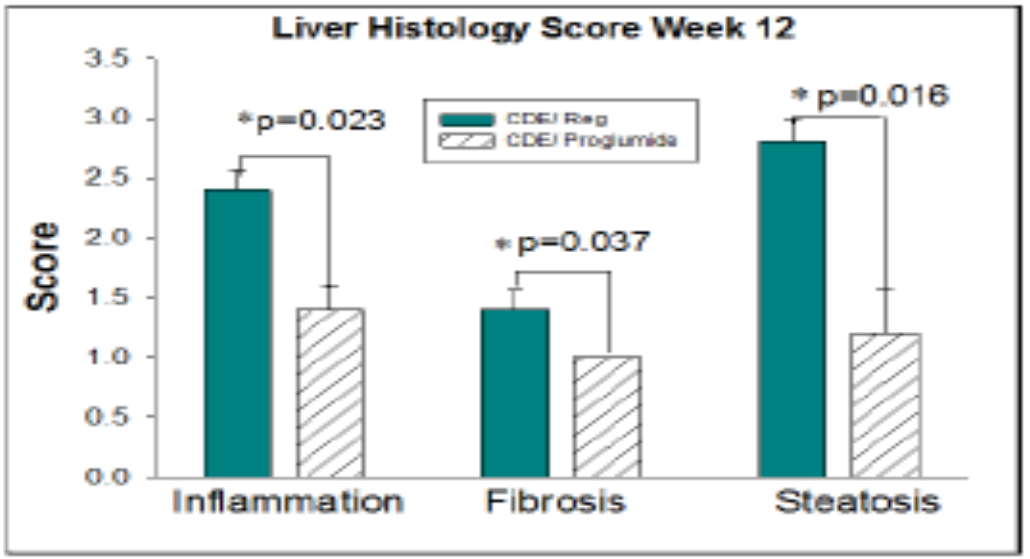
Study design



Proglumide reverses NASH

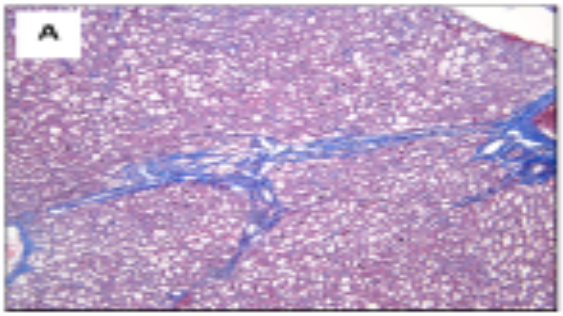
Proglumide reverses NASH in CDE mouse model



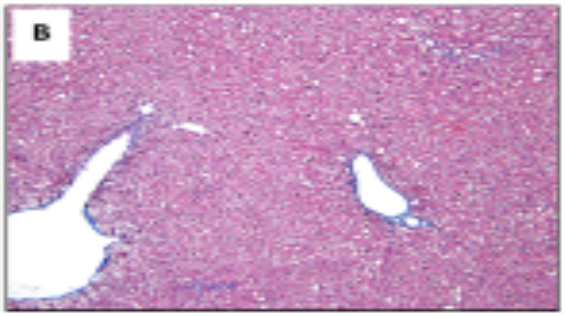


Control

Proglumide



Control



Proglumide

Phase 1 trial

Phase 1 Clinical Trial NASH

Repurposing an old drug: proglumide

Dose finding and safety study

Plans Phase 2 trial NASH

Phase 2 trial in cirrhosis to prevent liver cancer

Current trial ongoing in NASH (NIH/ NCI)
www.clinicaltrials.gov
NCT04152473

Smith lab